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SECTION I

The Pineal Gland and Its Diseases

The Anatomy, Embryology, Comparative Anatomy and Histology of the Pineal . . . . . *E. V. Cowdry*

Anatomy—Gross Morphology and Relations—Embryology—Comparative Anatomy—Histology. [From the Anatomical Laboratory, Peking Union Medical College.]

The Anatomy, Embryology, Comparative Anatomy, and Histology of the Pineal

E. V. COWDRY

NEW YORK

Anatomy

The pineal body derives its name from the Latin, *pinealis,* a pine cone, which it resembles in shape.

Gross Morphology and Relations.—It is attached by a short stalk to the posterior boundary of the dorsal surface of the third ventricle (Fig. 1).

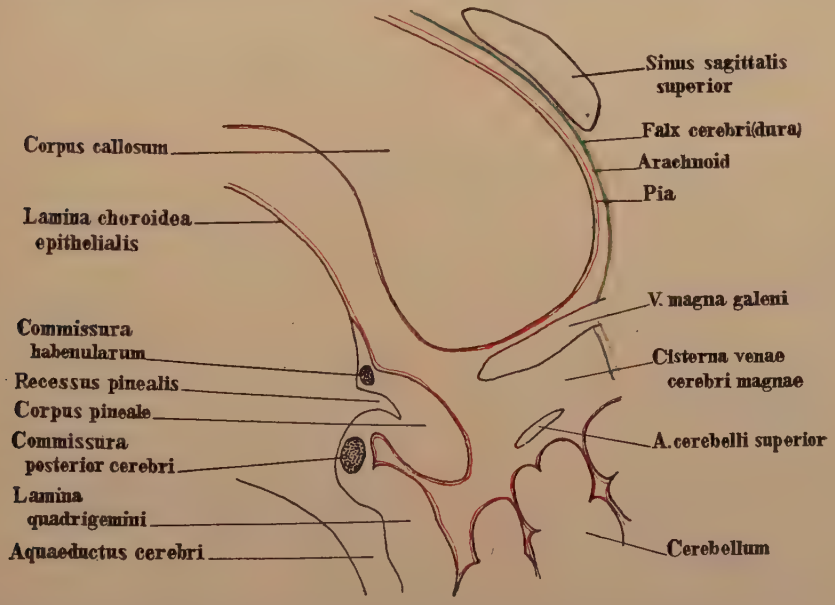


Fig. 1. Diagram of the relations of the human pineal body with dura, yellow; arachnoid, green; pia, red.

The cavity of the ventricle extends for a short distance into the stalk, forming the recessus pinealis. It rests on the midbrain, in the de-

pression between the superior colliculi, and is covered over with pia. It is dark red in color and measures about six millimeters long and four millimeters broad. The body is popularly considered to be larger in women than in men, but careful studies on rats have failed to reveal any sex differences (Hoskins(*b*)). It is, however, relatively larger in children than in adults.

Embryology

The pineal body first makes its appearance during the fourth or fifth week of development as an outpouching of the roof of the diencephalon just cephalad to the posterior commissure. It is formed first of ependyma only, but the walls soon thicken and mesodermal elements become included. It attains its highest development in children of about seven years of age, after which involutionary changes begin to take place.

Comparative Anatomy

From the standpoint of comparative anatomy, the pineal body, like the paraphysis, is simply a dorsal evagination of the neural tube. In some lizards it becomes highly specialized and may perhaps function as a rudimentary eye. It is never, at any stage in phylogeny, associated with the alimentary tract, but invariably develops from ectoderm which possesses sensory rather than internal secretory potencies.

Histology

In the fully developed condition the pineal body consists of scattered ependymal cells in a framework of neuroglia and connective tissue. The ependymal cells tend to be arranged in lobules, which are partially marked off by septa penetrating into the organ from the pial investment. Within the lobules cyst-like structures may be recognized and a variable amount of acervulus, or brain sand, is met with. The nerve supply is said to come from the optic thalamus. The blood vessels invade the pineal body with the connective tissue. They are large and sinusoidal. The ependymal cells are of irregular shape. They contain a good deal of pigment, as well as some lipoid inclusions and typical mitochondria. The reticular or canalicular apparatus has not been investigated. Except when the cells are arranged in the walls of cysts, there is no suggestion whatever of polarity. No secretion antecedents have been found. A careful study made with modern methods of technic is much needed.

A complete review of the literature up to 1915 is given by Studnicka. Some investigators are inclined to interpret the high vascularity, lobula-

tion, pigment formation, and so on, as evidence of an endocrin function. This has been questioned on histological grounds by Jordan(*b*); and Dandy and others have shown that experimental extirpation is not followed by characteristic symptoms. Repeated attempts to vary experimentally the activity of the pineal body, and to find corresponding structural modifications in it have invariably proved disappointing.

Physiology, Physiological Chemistry and Experimental Pathology . . . . . *Carey P. McCord*

The Pineal Problem, Past Views and Present Aspects—Administration of Pineal Material—Feeding Experiments with Pineal Glands—Feeding Experiments with Mammalian Forms—Experiments with Tadpoles—Feeding Experiments in Human Subjects—Influence of Pineal Extracts on Rate of Division of Unicellular Organisms—Injection Experiments—The Effects of Experimental Extirpation of the Pineal Glands—Sarteschi's Experiments—Exner and Boese's Experiments—Foà's Experiments—Biedle's Experiments—Horrax Experiments—Dandy's Experiments—Assaying Pineal Materials—Chemistry of the Pineal.

Physiology, Physiological Chemistry and Experimental Pathology of the Pineal Gland

CAREY P. McCORD

CINCINNATI

The Pineal Problem, Past Views and Present Aspects

The evidence that indicates for the pineal body a glandular function is much less definite than for such glandular organs as the thyroid, hypophysis, parathyroids and suprarenals.

Doubt is frequently expressed that the pineal body is more than a functionless vestige of what was once, in earlier evolutional stages, a functioning eye. Certain observations have led to the contention that the pineal body, through metamorphosis, has become a highly specialized tissue that serves the body in a manner comparable with the major members of the endocrin system.

Although the pineal forms a portion of the roof of the third ventricle, it is essentially a detached portion of the brain. A recognition of this fact is necessary to appreciate the early physicians' conception of its function. To them the structure was a movable organ, standing guard between the third and fourth ventricles, serving as a valve to control the flow of fluid from the brain to the spinal cord. However, so early an observer as Galen conceived a function of the pineal other than a mechanical one, for he writes: "It is in substance glandular and was devised for the same purpose as the other glands of the body."

Morphologic studies have been prosecuted in the main to determine: (1) the presence of glandular tissue, presumptive of a secretory function; (2) the presence of contractile tissue, supporting the view that this organ is a valve regulating the flow of cerebrospinal fluid; (3) nerve fiber communication between this organ and other portions of the brain, and (4) evidence of involution changes in the gland, indicative of a cessation or lessening of function.

The chief stimulus leading to systematic experimental investigations to ascertain the functions of the pineal gland as a factor in normal growth

and development, is the peculiar abnormalities of growth and development observed in young children, suffering from tumors of the pineal region. The general background of clinical manifestations that have served to initiate experimental investigations is summed up in the statement of Frankl-Hochwart: "When one finds in a very young individual, along with the general symptoms of tumor, as well as the signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor."

The further portion of this chapter is an evaluation of the scientific reports of physiologists, chemists, and experimental pathologists, to determine to what degree experimental evidence supports the clinician's conception of the pineal's functions. These reports are based upon investigations prosecuted along three general lines: (1) the administration, orally or hypodermically, of pineal gland preparations followed by observations of any changes induced by pineal constituents; (2) the extirpation of the pineal gland, followed by observations as to the results of the deprivation of whatever substances the gland may elaborate, and (3) chemical analyses and physiologic assays of the glandular material with the aim of obtaining active principles in purified form.

I

Administration of Pineal Material

Preparation of Materials.—For extensive work, the procuring of sufficient material in suitable form is not without difficulty. The weight of the individual gland in cattle is about 0.2 gram and in sheep about 0.15 gram. As will be noted subsequently, glands from young animals yield better results; making use of the pineal gland of calves, it will be found that approximately 3200 are required to produce one pound of the fresh glands, which, on desiccation, lose approximately six-sevenths of their weight, yielding slightly over 2 ounces of dried material. To produce a pound of dry pineal substance, approximately 25,000 animals are required.

The materials used by various workers for feeding experiments, and for hypodermic administration have been prepared in many respects by similar procedures.

Desiccated Preparations.—Without, at this time, making detail references to trivial innovations by different investigators, the method for preparing a usable desiccated pineal substance may now be described:

(1) Only fresh glands are desirable. Being nerve tissue, deterioration is rapid. If glands are shipped for a long distance, they should be frozen *en masse* prior to shipment.

(2) The cleansed glands are minced to a smooth paste in a grinder of the Latapie type.

(3) For usual purposes, it is desirable to avoid extraction with any fat freeing substance such as benzin, ether or acetone, inasmuch as there are some reasons for the belief that active substances are contained in the lipoid fraction of the glands.

(4) Thin layers of pineal paste are spread on granite trays and quickly desiccated in a vacuum dryer with heat not exceeding 70°C.

(5) After a few hours the material is completely dry, and scales easily from the granite trays.

(6) The pineal material is now in flat lumps. It may be reduced to a fine powder by grinding in a ball mill, or by hand in a mortar.

(7) This simply prepared material if kept very dry will not appreciably deteriorate. For ease in administration it may be diluted with milk sugar, in the approximate ratio of four or six parts of sugar to one of glandular substance, and made into tablet triturates.

Liquid Preparations.—Those workers who have employed liquid extracts in hypodermic or intravenous administrations, usually obtain their material in small quantities through the saline extraction of freshly mascerated glands, or through the saline extraction of the powder prepared as noted in the foregoing description. Without special precautions, liquid preparations deteriorate rapidly. The protein content may grossly be removed by acidulating with a few drops of diluted acetic acid followed by heating to 90°C. By placing the extract in small ampules (1 c.c.) and heating to approximately 95°C. for 1 hour, the preparation may be protected from appreciable deterioration. By custom, actual boiling of extracts is avoided in the belief that part of the activity is thereby impaired. The evidence leading to this conclusion is scant and actual boiling for sterilization might prove practical and desirable.

Feeding Experiments with Mammalian Forms.—If the pineal gland is an organ serving the body through the elaboration of active chemical substances, it is rational to anticipate that these substances contained within the glands may, when fed to animals, induce a condition analogous to hyperpinealism, through providing for the body's utilization additional pineal constituents.

The syndrome of precocious development seen in man is usually interpreted as the outgrowth of pineal deficiency, i. e., of hypopinealism. Such being the case, if the feeding of pineal materials determined any changes, a state just opposite that cited above would be anticipated—a condition of deferred sexual, mental and somatic maturity. Curious to record, feeding experiments lead either to no determined effects or to increased sexual and somatic development.

Earlier Feeding Experiments.—Dana and Berkeley carried out the

first recorded feeding experiments. For this work they made use of kittens, young guinea pigs and rabbits as test animals.

"Of eight halfgrown guinea pigs, well fed (an excess of bread and fresh cabbage, no water), in an airy and well lighted room, under observation for five weeks, all in the same cage, four received intraperitoneal injections, three times a week, of pineal nucleoproteid, and four were kept as controls. The dose of nucleoproteid was fifteen minims of a solution of which one ounce represented thirty calves' glands. The controls gained 25 per cent in weight, the subjects gained 36 per cent. The difference was perceptible to the eye, and the subjects could be picked out by persons not knowing which had been injected.

"Of twelve small kittens, selected at random from tenement backyards, six were fed on calf's pineal, and six were kept as controls. The subjects outgrew the controls rapidly in activity, size, intelligence, and resistance to intercurrent disease. The best control, beginning with a weight of 11 ounces, gained 4 ounces in two months and a half. The best subject, starting with a weight of 12 ounces, gained 12 ounces more, doubling his weight. The food was milk and raw meat. The medication for the subjects was fresh gland—one calf's gland apiece per day, or thirty minims of a standardized solution of nucleoproteid in the milk.

"Twelve small guinea pigs, laboratory bred, were selected for a third experiment. Six were fed for four months on the pineal substance, approximately 5/8 grain three times a week, and six were kept as controls. The subjects (average of five surviving) increased their weight 325 per cent; the controls (average of four surviving) increased their weight 250 per cent.

"Ten small rabbits were selected for a fourth experiment. They were of varying color and size, and did not appear to be of the same parentage. They were under observation for five months. Of the five pineal fed animals, one died. The four survivors, weighing *in toto* at the beginning of the experiment 2975 grams, gained in the period mentioned a total of 5770 grams, or an average of 1442.5 grams per rabbit.

"The five controls met with various accidents in the period of experiment, and the three survivors at the end of the time had gained in all 3223 grams, or an average gain of 1074 grams per rabbit. The subjects were beautiful specimens—clean, fat, active and salacious. The gain they made is certainly remarkable. One of the smaller ones trebled his weight exactly."

The Author's Feeding Experiments.—McCord(*a*), in 1914, continued the investigation. After some preliminary experiments in feeding young chicks, guinea pigs were adopted as test animals. A lot of fifty in the second week of life was selected and divided into test and control groups. The test animals were daily fed 10 mgs. of desiccated calves' pineal tissue. The control animals were fed equal quantities of milk sugar. Other con-

ditions for the two groups were identical. At the end of ten weeks the pineal fed group had gained 23 per cent in excess of the control group.

This excess in weight of pineal fed guinea pigs over their controls was a symmetrical overgrowth. There was some increased adipose tissue, but this was generally distributed and not localized in any one region of the body. At no time was it possible to continue this excessive growth above normal adult size. As the animals approached adult size the pineal feeding became less effective, and after full maturity was attained, was without further effect. There was no tendency to gigantism.

Investigation of Precocious Sexual Development from Pineal Feeding. —In view of the supposed relationship between the pineal body and *puber-*

Fig. 1. Effects on the growth of young guinea pigs of feeding with small quantities of pineal glands. Larger, sleeker animals on right, pineal fed; animals on left, controls. Average animals from a series of 50. Pineal fed animals were 23 per cent larger than controls in ten weeks. (From McCord, J. Amer. M. Ass., Chicago.)

tas precox, experiments were carried out to determine whether any relation might be demonstrated between pineal feeding and precocious sexual development. A group of forty-eight guinea pigs was divided into test and control lots. There was an equal number of males and females in each lot, but the males and females were separated. The test pigs were fed calves' pineal tissue in 10 mg. amounts daily. Feeding was begun when the animals were two weeks old and continued for nine weeks. The males and females of each group were then placed together in breeding pens. As a measure of any difference in sexual development it was thought desirable to note the date of birth of young in the two lots. All except two of the pineal fed animals gave birth to young, before the first of the controls. Fourteen days elapsed between the birth of the young of the first pineal fed, and the first control animals. In all cases the young were normal and in no wise different from any other young guinea pigs.

Conclusions from Author's Experiments.—The results of this work led McCord to the conclusion that the administration of minute quantities of pineal tissue, from young animals to young animals, stimulates rapid growth of the body, but not beyond normal size. Also there were indications of precocity of mental and sexual development, but these were less well established.

The data, arising from two years of feeding experiments with pineal substance, are sufficiently extensive to render insignificant the operation of any accidental vitiating factors. Averages of a number of experimental series, aggregating nearly 400 animals, would indicate that young animals to which had been administered pineal tissue, developed at a rate in excess of normal controls.

The most pronounced results arose from the feeding of young animals with material derived from young animals.

Although some histologic evidence exists indicating the glandular nature of the pineal in mature adult life, such material, when fed to young animals, did not bring about the changes observed in feeding with younger pineal material. As previously stated, at no time has gigantism been produced. As adult life is approached, pineal feeding is less effective.

The excess growth of young animals under pineal feeding is essentially symmetrical. No disproportion has been observed except a possible hypertrophy of the testes noted in some animals. In microscopic sections, such testes are seen to be made up of larger and more mature tubules than in controls of the same age, but with no increase in the interstitial tissue.

Both males and females are affected by pineal administration, but the gains (in relation to respective controls) have been greater for males than for females.

Negative Experiments with Rats.—Hoskins, in a series of feeding experiments with various endocrin glands, administered pineal substance to albino rats. The rat would seem, in many respects, better suited for feeding studies than any other small animal, because precise investigations have been made as to normal variations in all organs and portions of the rat's body. The white rat is a standardized laboratory animal. No evidence was developed in Hoskins' work that the pineal feedings in any way affected the growth of his rats.

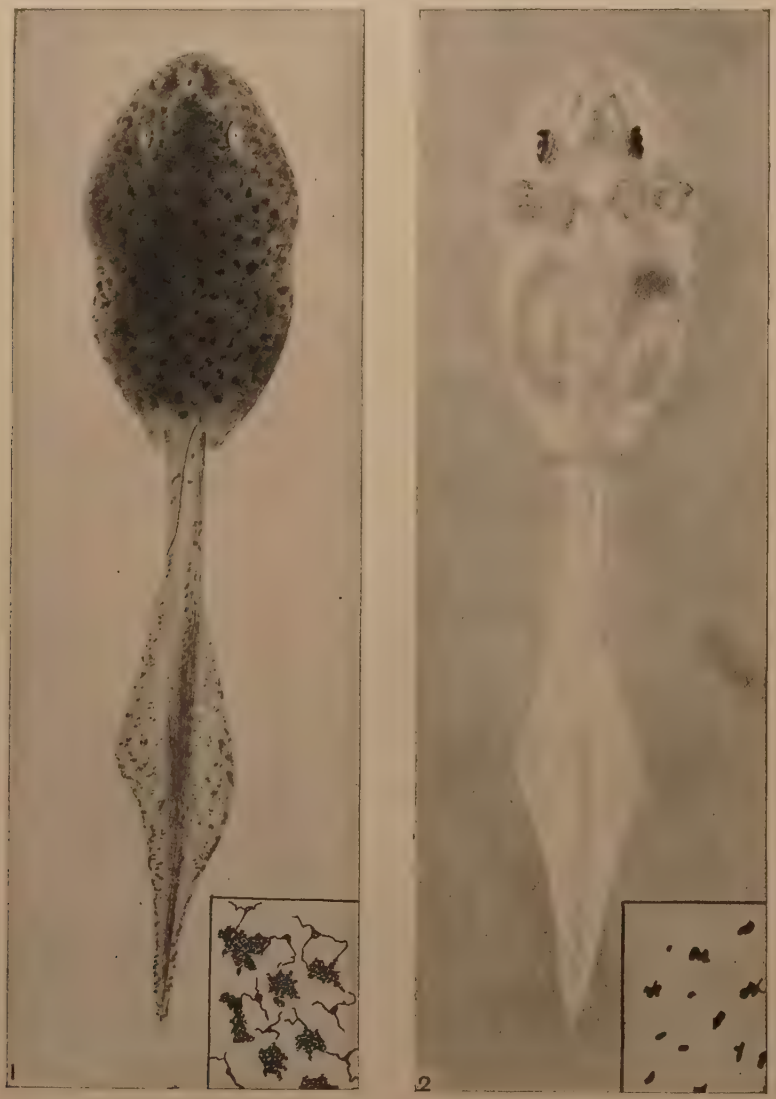
More recently, Sisson and Finney have reported the results of a similar investigation with white rats. Their animals were from the carefully bred Wistar Institute stock. Fourteen experimental animals and ten controls made up their series. The experiments were carefully conducted, both sets of animals being kept under identical conditions and the controls given casein to compensate for the pineal substance fed to the experimental group. The best of hygienic and dietary conditions were maintained. Pineal glands from calves were desiccated and administered in dosage from

0.01 to 0.05 gm. Their results, like those of Hoskins with white rats, were essentially negative. The only variation from the normal, noted either grossly or histologically, was a slight retardation of growth in a few cases. Whether these negative results are to be explained by the fact that the gland material used was previously extricated with ether, remains to be determined. The possibility of such procedure introducing a vitiating factor was earlier mentioned.

Experiments with Tadpoles.—*The Influence of Pineal Extracts on Alterations in Pigmentation.*—The well known color changes in many life forms are obviously in adjustment to environmental conditions. The eye is the essential controlling factor in this adjustment. When in blinded animals certain definite changes in pigmentation still occur, on *a priori* grounds, it is tenable to assume that the pineal body retains sufficient ocular mechanism to exert its influence upon the pigment cells. This is the hypothesis suggested by Fuchs(*b*) in his elaborate monograph on "Der Farbenwechsel und Chromatische Hautfunktion." Many acceptable observations indicate an association between the pineal gland and an earlier optical function. In the reptilian stage of evolution, the pineal as a parietal eye probably attained to its highest development. In the embryos of certain lizards (Lacerta agilis), the typical eye structure is still evident, but in no form, living at the present time, does the pineal gland retain an ocular function of high order. Laurens has established experimentally that Fuchs' theory as to the rôle played by the pineal in pigment changes in relation to the environment is highly improbable. Accepting the contentions of Laurens, McCord and Allen reported that although the pineal does not act in the rôle of its ancient ocular precursor, it contains within itself an active principle capable of inducing pigment changes independent of, and wholly apart from, environmental conditions. The pineal pigment changes dominate and appear despite environmental conditions tending toward the opposite phase.

These workers, in 1915, noted pigmentation alterations in connection with their experiments on the influence of the pineal gland substances upon growth and differentiation processes in tadpoles. On the tenth day of larval life, it was readily observable that in the pineal fed tadpoles the coloration was uniformly lighter than in the control, muscle fed groups. This alteration was at first attributed to some unknown difference in environmental conditions—light, background, etc., since the color of these organisms was known to vary considerably in relation to such conditions. These changes when first noticed were trivial in degree, but as development progressed, the alterations in pigmentation became correspondingly greater. Thirty minutes after feeding pineal tissue, the tadpoles which prior to the feeding had been uniformly dark, became so translucent that all the larger viscera were plainly visible through the dorsal body wall. This translucency appeared with such regularity and so punctually after pineal feedings,

and was so markedly absent in the control groups, that the phenomenon was made the subject of special study.



2 3

Figs. 2 and 3. Drawings of the same tadpole (Rana pipiens) just prior to (Fig. 2), and forty-five minutes after (Fig. 3), pineal feeding, showing the transient loss of pigment due to action of pineal constituents on the melanophores. Inserts in lower right hand corners show appearance of melanophores in each condition. (After McCord and Allen, J. Exper. Zool.)

Eggs of the species Rana pipiens, Rana cantabrigiensis and Bufo americana were collected in the vicinity of Detroit, and hatched in the labora-

tory. Immediately after hatching, and before the oral orifice had opened, they were grouped in trays into colonies of 200, and food was placed in the trays. The food was weighed, each colony receiving the same amount triweekly. All foods were taken voraciously by the tadpoles. By means of a water dropping and disposal system, the tadpoles were kept at all times in fresh, aërated tap water. Moreover, the trays were frequently shifted to average environmental conditions of light and temperature. In the observations on pigmentation, some 12,000 tadpoles were used.

The food consisted of desiccated glandular material and fresh plant food. Of the glands, the effects of pineal (adult and preadult), thyroid, parathyroid, and suprarenal were tested. Brain tissue and beef muscle were used as controls. Different lots of tadpoles were fed upon Spirogyra, bread crumbs and hemp seed as a further check. A single lot of tadpoles was fed on desiccated retinæ from beef eyes as a particular experiment. Of these tissues the pineal gland alone produced the phenomenon characterized as the pineal pigment cycle.

After the tenth day of larval life, pigment changes were always evident after every feeding of the pineal tissues, and the animals continued to react until the age when their forelegs protruded. Sufficient blanching of the bodies occurred, within thirty minutes after pineal feedings, to differentiate these colonies from their controls. A maximum condition of translucency was attained in about forty-five minutes, and three to six hours later restoration of the original color was complete. The difference was first noticeable in the region about the eyes, due to the absence of larger viscera. It can be demonstrated, however, that the reaction occurs simultaneously over the whole body. At the height of the reaction, the integument was so transparent that the brain, the olfactory tracts, the kidneys, the beating heart, and the intestines were all clearly visible through the dorsal body wall.

Figures 2 and 3 are drawings of a single tadpole, just prior to, and forty-five minutes after feeding pineal material. The darker portions in 3 are due to the denser viscera, the pigment conditions being the same over the entire animal.

These described alterations in pigmentation are invariably induced in tadpoles upon the administration of pineal materials, be they the fresh minced glands, simple desiccation preparations, simple aqueous extracts, or certain lipoderivatives of the glands.

This pineal depigmentation was shown to be due to the clumping into small spheres of the pigment granules which under normal conditions are evenly distributed throughout the melanophores.

Feeding Experiments in Human Subjects.—Following the establishment that pineal extracts when fed to animal subjects stimulate an increased cellular activity, there arose the high hope that this substance might prove efficacious in activating the undeveloped, dormant cells in

children, who were mentally or physically retarded. Abundant data had made clear that such medication was without deleterious effects. The first of these studies was made by Goddard and Cornell in 1913. In addition to their own work they report the results of similarly planned studies which were carried out by Dana and Berkeley among the defective minded school children of New York City.

Goddard and Cornell selected twenty-five mentally defective children, chosen as far as possible from the younger groups, some of each sex, and of different grades of intelligence from the lowest to the highest. Careful examinations were made as to mental age, etiology of mental defect, height, weight, grip, lung capacity, etc. A control group of twenty-five other mentally defective children was so chosen that each child to be fed glandular materials was paired with a control child of as nearly the same age as possible, physically and mentally, with similar family histories, and of approximately the same state of development. The same careful preliminary tests were made on the control group as on the test group. It was duly recognized with reference to controls that no two children are exactly alike in temperament, mental or physical condition.

The material used as the therapeutic agent was the glands from young bullocks. The glands from twelve bullocks were so desiccated as to prepare one hundred capsules of medicament. The dosage was approximately $\frac{2}{3}$ grain of wet weight gland per capsule. One capsule per day was the initial dose. At the end of two months of feeding each group was carefully reëxamined. The results indicated a very slight advantage in favor of the pineal fed children. This was shown in mental capacity, and physical development except gross weight which was slightly reduced. While the improvement was not great, it was held as significant enough to warrant the continuation of the work. At the end of the four month period of feeding, their results are thus summarized:

As a group the twenty-one subjects had gained 2.23 points. Of the fourteen who gained, the average mental gain was 3.35 points. The fourteen controls gained as a group 1.35 points mentally. Of the nine who gained, the average mental gain was 2.11 points.

The subjects in seven groups gained from four to nine points mentally. In each group in which there was any mental advance the children had the mentality of three years or more. Those in the idiot group had not improved mentally.

Physical Development.—The gain in the standing height for the twenty-one subjects averaged 18.52 mm.; for the fourteen controls, 24 mm.

In weight the twenty-one subjects gained an average of 2.06 kg., the fourteen controls, 2.89 kg. There was no loss of weight in either subjects or controls.

In right hand grip, the twenty-one subjects gained an average of 0.9 kg. as a group, and the twelve who gained average 1.58 kg. The fourteen

controls gained an average of 3.43 kg., the ten who gained averaged 4.8 kg.

Goddard in 1917, reporting upon the final results of pineal feedings of this same group, concluded that ultimately the entire findings must be considered as negative.

Although, shortly after the institution of feedings there are measurable indications of mental stimulations in some instances, these do not further develop with continued treatment. It is not believed that any of the studies made afford evidence of a therapeutic value of pineal feeding.

Influence of Pineal Extracts on Rate of Division of Unicellular Organisms.—As pointed out by McCord(*c*) in 1917, all feeding experiments

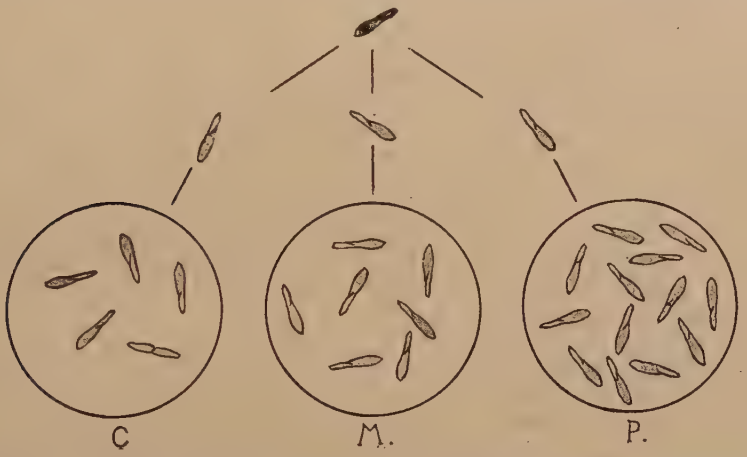


Fig. 4. A diagram showing influence of pineal extracts in accelerating the division rate of paramecia. Diagram represents the average of thirty-six experiments. Full description in text. (After McCord, Trans. Amer. Gyn. Society.)

with such unstandardized animals as guinea pigs, chickens, dogs, cats, etc., are open to objection in that normally such subjects exhibit very appreciable individual variations. To obviate this error McCord investigated the action of pineal extracts upon less complex life forms that show scant individual variations and are obtainable in large numbers. For this purpose was chosen the Paramecium caudatum, a unicellular organism that may divide into many generations in a single day.

Cultures were maintained in the laboratory, growing on hay infusions. These organisms are about $\frac{1}{4}$ mm. in length and may readily be counted with the naked eye. Reproduction is accomplished through transverse splitting. Under standardized conditions the rate of division is relatively constant. It was assumed that, in the event of constant exceptional variations in the number of generations formed when pineal materials were added to the culture medium, and not occurring when other similar protein materials were introduced, that the phenomenon would be attributable

to pineal activity. The following procedures were employed. A single paramecium was isolated until the reproduction of the third generation. These resulting four individuals were separated and placed in different media: (a) one in hay infusion; (b) one in hay infusion plus extract of desiccated pineal gland, 0.05 per cent strength; (c) one in hay infusion plus extract of desiccated muscle of equal strength, as a control material, and (d) the fourth one was a variable control. These cultures were maintained in a moist chamber for a fixed period (forty-eight or twenty-four hours). At the expiration of that time the several cultures were examined as to the number of reproductions. Almost invariably, the divisions were more numerous in the pineal culture. For example, in one forty-eight hour experiment, twelve offspring resulted from the plain hay infusion, thirty offspring resulted from the hay infusion plus pineal extract and ten offspring from the hay infusion plus muscle extract. The results from thirty-one consecutive experiments are grouped in Table I.

TABLE I

RECORDS OF DIVISIONS OF PARAMECIA, IN VARIOUS MEDIA. FIGURES INDICATE NUMBER OF OFFSPRING FROM SINGLE PARENT ORGANISM IN EACH CASE

48-Hour Group				24-Hour Group			
No. of Expe'm't	Hay Infusion	Pineal Gland	Muscle Tissue	No. of Expe'm't	Hay Infusion	Pineal Gland	Muscle Tissue
1	7	23	..	18	7	13	..
2	7	31	..	19	3	6	..
3	11	12	..	20	11	19	..
4	5	8	..	21	3	5	2
5	1	16	..	22	4	8	8
6	1	13	..	23	6	16	4
7	4	12	..	24	4	8	5
8	5	19	12	25	10	17	10
9	5	12	9	26	11	19	..
10	13	12	4	27	4	7	5
11	2	9	4	28	1	4	3
12	2	7	6	29	1	7	2
13	3	19	16	30	3	8	2
14	1	21	12	31	5	15	5
15	10	25	23				
16	12	30	10				
17	13	22	11				
Average ..	6.0	17.1	10.7		5.0	10.5	4.6

The inference is, that pineal materials, when added to the culture medium of the unicellular organism, paramecium, determines a more rapid rate of reproduction.

Injection Experiments.—*Immediate Results Following the Intravenous or Subcutaneous Administration of Pineal Extracts.*—Unlike the intense cardiovascular action of suprarenal extracts, or the uterine contract-

ing action of pituitary extracts, the immediate results from intravenous or hypodermic injections of pineal extracts are not pronounced. Such phenomena as decrease in arterial tension, dilatation of the bloodvessels, altered amplitude and rate of the heart beat, diuresis, glycosuria, and uterine contractions have been reported and confirmed.

Howell was the first to make mention of intravenous injections. In 1898, he administered pineal extracts as controls in experiments upon the action of pituitary extracts. Apparently the results were such that no significance was attached to the experiments. Von Cyon in 1903, using rabbits as subjects, made a study of the action of pineal extracts prepared from ox and sheep glands. This worker reported that such extracts were without definite effect upon the blood pressure. Following small doses, he observed a tachycardia associated with a feeble pulse, which he attributed to the presence of certain inorganic salts contained in the gland. At the time of this publication, he concluded that the function of the pineal is purely the mechanical one of controlling the flow of fluid through the aqueduct. Dixon and Halliburton in 1909, in further experiments of this type, employed extracts made up from a preparation of desiccated sheep pineal glands. The dried glands were extracted with various solvents and the extracts injected intravenously into cats. No mention is made as to whether these glands were obtained from young or adult animals. Very small doses were employed, and from these scant evidence was obtained of any action. On using larger doses a transient fall of blood pressure occurred, but no changes were reported to have occurred in heart rate or amplitude, respiration, intestinal or kidney volume. In 1912, Ott and Scott in several papers on internal secretion referred to experiments with pineal gland extracts. Noteworthy are their observations that pineal extracts induce vasodilatation in the erectile tissue of the generative organ of the male cat, stimulate the contraction of the intestinal wall and uterus, produce a slight diuresis and glycosuria and increase the activity of the mammary gland.

By far the most exact study of the immediate effects of pineal extracts was made by Jordan and Eyster (1911). The material employed was sheep's pineal glands, either freshly prepared or preserved in alcohol or formaldehyd. The amount constituting a dose was usually the extract from one gland given intravenously. Their own summary, here appended, gives the scope of their work and their conclusions:

"Our experiments indicate that the pineal gland of the sheep contains some substance (or substances) which, on intravenous injection in certain animals, causes a fall of blood pressure associated with vasodilatation in the intestines, produces a slight degree of improvement in the beat of the isolated cat's heart, and causes a transitory diuresis associated with glycosuria in about 80 per cent of the cases. We have found, in agreement with Dixon and Halliburton, that the effect on blood pressure in the

cat is small and unimportant. It should be noted that our extracts were in all cases more concentrated than those employed by these investigators. On the whole, our work would seem to indicate that while certain definite effects on the circulation and secretion of urine are produced in certain animals, as the result of intravenous injections of extracts of the pineal body, the action is relatively slight when compared with that produced by extracts from other glands known to furnish internal secretions.

"Our experiments obviously deal with only a possible rôle of the pineal body in producing certain relatively rapid effects on the circulation, respiration, and secretion of urine. They leave entirely untouched the possibility of more gradual effects over longer periods of time, as well as the influence these bodies may exert on metabolism or other functions and their relation to other organs of internal secretion."

In Dana and Berkley's report (1913), which has been considered in detail in the section on feeding experiments, reference is made to some cardiovascular studies. The following is a quotation summarizing their findings:

"The blood pressure experiments were virtually negative. Two dogs were used. The first dog received in rapid divided doses, intravenously, a concentrated solution of the nucleoproteid extract of thirty calves' glands. There was no response. The same animal then received intravenously 2 oz. of the globulin-albumin content of the same glands without results. The second dog received a concentrated, filtered, saline solution of twenty-four bullocks' pineals, with no essential response."

With the idea that extracts of very young animals might be more potent than those commonly employed, a series of observations was made by Horrax with glands from calves and young sheep. The material was obtained fresh from the abattoir, ground up in a mortar and dried in the air. A part was mixed with lactose in the proportions of 1:3, and when used was weighed out as powder and dissolved or taken up in normal salt solution. Medium sized dogs were used and the injections were made into the left external saphenous vein.

Injections of small amounts (0.1 gm.) gave practically no result. There was a variable, moderate fall in blood pressure, with no effect on respiration or on the flow of cerebrospinal fluid. With larger amounts of the powder (0.5 gm.) a constant fall in blood pressure was recorded, varying from 10 to 24 mm. of mercury. The immediate effect of the injection lasted on the average about two minutes, the pressure in all cases showing a subsequent gradual rise to normal over a period varying from ten to fifteen minutes; in no case was there a subsequent pressor response.

In order to test the effect on the flow of cerebrospinal fluid, the Cushing-Weed method of puncturing the third ventricle was employed, each drop, as it fell from the cannula, being recorded by a marker on the drum. The effect on the cerebrospinal fluid was that which might be expected

merely from the concomitant fall in blood pressure, namely, a slowing of the flow, or in some cases an absolute stoppage. The injections made with extracts of the fresh glands before drying, either by boiling or extracting in warm salt solution, were in all essentials similar to those with the dried powder. In order to see whether the effects recorded were due to the pineal extract itself, or to the cholin content of the gland, 1/300 grain atropin was used in a series of injections along with the pineal extract. The results obtained from these injections varied considerably, but in all cases a slight fall was demonstrable and, in at least one case, the fall was measurably as great as that caused by an injection of the extract without the atropin fifteen minutes previous. Horrax has found, therefore, in agreement with his predecessors, that intravenous injections of the extracts of the pineal body of young animals cause a constant but relatively slight fall in blood pressure. The injection causes no increase in the flow of cerebrospinal fluid and the fall of blood pressure, moreover, is not due entirely to the cholin content of the gland.

McCord(*b*) (1915) carried out twenty animal experiments in which pineal extracts were injected into the jugular veins of dogs anesthetized with chloretone. The pineal extracts were prepared from fresh glands by grinding in a mortar with saline solution. The usual dose was one gland in 2 mils of solution. The results obtained were contradictory. Some of the dogs were quickly killed by a single injection of the extract from one gland. The phenomena associated with the injection were a rapid and marked fall in blood pressure, depressed and irregular heart and intense venous engorgement, followed by death. However, in the larger number of animals it was found that a dose of one, two or more glands prepared in the same manner brought about no observable effect.

In general, it may be maintained that the immediate results attending the intravenous administration of extracts from the pineal gland are not usually pronounced. The intensity of the several activities reported as occurring is so slight that at the present time no great significance may be attached to them. In the light of Abel and Kobota's findings, that in all tissue of the body histamin is present, practically all of the immediate results following pineal administration may be attributed to the small quantities of this amin contained in the gland.[1]

[1] Vincent has stressed the fact that such observations as those quoted cannot be given any weight as evidence of hormone content in the extracts. Similar results—whether due to histamin or not—can be obtained with a variety of extracts, including quickly prepared extracts of the experimental animal's own glands.—R. G. H.

II

The Effects of Experimental Extirpation of the Pineal Gland

On the assumption that the clinical syndrome, such as reported by Heubner and by Ogle, as incident to pineal tumors, is due to neoplasms destructive to the pineal gland which thus deprive the body of this organ's functions, it would be reasonable to expect that similar changes would follow the experimental removal of the pineal. As a matter of fact, extirpations have been attempted in various animals with the employment of varied technics, but the results are far from conclusive. The pineal is so deeply situated, so intimately associated with important and easily injured structures that its removal by operation is attended with the greatest difficulties. As pointed out by Dandy, the greatest danger encountered in the removal of the organ is hemorrhage, and especially hemorrhage into the ventricles. From its inaccessibility the definite recognition of the gland in a field of operation is most difficult. Prior to the work of Dandy and Horrax the practice appears to have obtained of operating on large numbers of animals in the hope that a few might survive. In one series the mortality was seventy-five out of ninety-five operated upon; in another twelve out of fifteen. With so high a death rate, it may be questioned whether the few survivors would exhibit constant changes referable to pineal deprivation. Among vitiating factors interfering with the proper interpretations of results due purely to pineal removal are, first, body changes due to the severe operative process necessary for the gland's removal; second, the comparison of results obtained from adult animals with those from young animals; third, on incomplete removal of the gland, inflammatory changes in the remaining functional part may increase the secretion of the pineal substances; fourth, intracranial pathological processes, incident to pineal ablation, may lead to disturbance in pituitary functions and thus complicate the attending body alterations.

Results from the experimental extirpation of the gland should lead to the answering of such questions as: (1) Is the operative removal of the pineal gland in animals feasible? (2) Is the entire gland or is any part of it essential to life? (3) What immediate changes occur on its removal? (4) If it is not essential to life, what remote changes, if any, occur following its removal, such as alterations in the general metabolism or disturbances in the other endocrin organs?

Sarteschi's Experiments.—In 1910 Sarteschi(*a*) attempted the destruction of the pineal in rabbits. Eleven animals were subjected to the procedure with fatal results in nine. In only one of the survivors was the pineal thought to be completely extirpated. The results were negative.

Later, however (1913), Sarteschi(*b*) reported the production of the "macrogenitosomatic syndrome" in young rabbits and puppies. Of twenty-three rabbits operated upon at the age of about forty-five days, three only survived, and in these, a small remnant of the pineal body was found on autopsy. Following pineal removal the testes were greatly hypertrophied, as in Foà's cockerels. The rabbits had up to the time of their death (at the age of five to seven months), grown much more than the controls of their own age. All the organs, including the endocrin glands, were normal. Sarteschi concluded that in rabbits pineal ablation, whether it be complete or incomplete, determines a more rapid development, sexual precocity and notable enlargement of the testes. In puppies the operation was found to be more difficult; out of twenty-seven only five survived. Operation took place at the age of two months. Substantially the same results followed as in the rabbits. The testes of one puppy were of adult size before he was five months old; at autopsy they were found histologically normal. Another male puppy showed, at the age of five months, unusual size and adiposity and enlarged testes. In conclusion, Sarteschi accepted Pellizzi's hypothesis that the pineal body exercises a moderating action on genitosomatic development.

Exner and Boese's Experiments.—These authors in a series of pineal operations made use of the cautery. Precise location of the pineal for cauterization is not possible, consequently the destruction of contiguous tissue was considerable and the attending mortality high. Seventy-five of the ninety-five animals operated upon died, the greater number from hemorrhage. Among the survivors no changes occurred attributable to pineal deprivation.

Foà's Experiments.—Foà(*a*), in 1912, after extensive preliminary work, from which he decided that the rabbit is wholly unsuited for pineal extirpation experiments, directed his attention to pineal ablation in young chicks, and reported the production in young cocks of precocity in body and sexual development. The glands were removed from the chicks at about one month of age. The mortality percentage was very high, only 25 per cent of his animals surviving. The females of the series evinced no indications of any changes due to pineal destruction, except a retardation in growth during the first two or three months subsequent to the removal of the gland. The three young cocks, which survived, according to Foà, showed excessive growth of combs and testes and exhibited indications of greater sexual activity.

Further experiments upon chicks and rats were reported by Foà(*b*) in 1914, to substantiate his earlier claims as to the pineal's functions. He thus summarized this recent work: "The new experiments on the extirpation of the pineal gland in the young male chick confirm the result which I previously obtained, that the operation is followed by a development of the testes and the crest greater than in the non-operated

control cock. The difference begins to manifest itself five months after the operation and increases constantly up to the ninth month. The operation produces no effect on the general development of the body in the fowl.

"The extirpation of the pineal gland, in the very young rat, produces no appreciable effect in the female; in the male it provokes a more rapid somatic development and the maximum difference is observed, between the weight of the operated animals and the controls, twenty-six to thirty days after the operation. Then the weight of the experimental animal gradually becomes equal to that of the control.

"At the moment when the difference in weight reaches the maximum, one observes also a markedly greater development of the testes in the experimental animal. The difference in the testes disappears when the weight of the body becomes equal.

"The histologic examination of the testes, in the cock as well as in the rat, at the time of maximum difference in volume, reveals a uniform development very advanced in all of the tissues of the gland; the diameter of the canaliculus is increased, the opening enlarged; the mass of spermatozoa which fills the canalicular opening is greater; the canaliculi are more separated from each other and, consequently, the interstitial tissue shows greater development. There is no difference in the spermatogenetic process, if one excepts the quantity of spermatozoa which fills the larger opening of the canaliculus.

"The canalicular tissue and the interstitial cells being uniformly more developed in the experimental animal, it is impossible to say that to any of these tissues is due the greater development of the secondary sexual character in the cock and the somatic development in the rat.

"The experiments on the rats have shown that the extirpation of the pineal gland does not determine an absolute hypertrophy of the testes, but a premature development of them. Forty-eight days after the operation, the operated rat cannot be distinguished from the control. This observation confirms the theory which attributes to the pineal gland an inhibiting function in the sexual development; we learn from this that with the beginning of puberty there coincides an involution of the pineal gland."

Biedl's Experiments.—Biedl stated in 1913 in regard to his work in removal of the pineal gland: "I have occupied myself for some time with experiments, the main object of which has been to determine the clinical results of pineal suppression. I have succeeded, so far, in extirpating the pineal gland by a method similar to that which I employed in hypophysectomy. As far as my observations go, the pineal gland in the adult animal is a negligible quantity; my experiments with young animals are not as yet complete."

Horrax Experiments.—Horrax in 1916 reported the successful removal of the pineal from guinea pigs and rats. The guinea pigs when

operated upon, varied in age from two days to six or seven weeks, and usually the experimental and control animals were members of the same litter.

On the whole, the animals did very well, considering that they were operated upon at so early an age, and if tided over the first forty-eight hours they usually lived until sacrificed, although a few of both experimental and control animals died after the course of several weeks, due to intercurrent causes. In all, 144 guinea pigs were operated upon, and of these an attempt was made in eighty-two to extirpate the gland, while in the remaining sixty-two a control trepanation was performed. The larger number of experimental animals is due to the fact that the operation upon them being more severe, there were more immediate casualties, necessitating a greater number of subjects for operation. Of the eighty-two experimental animals, forty-eight lived to maturity or until sacrificed, while of the sixty-two controls, forty-two lived an equal length of time as the corresponding experimental animals.

In nearly every instance, postoperative death was due to hemorrhage from the large vein of Galen. The mortality is necessarily high.

Results in Males.—As to results in the males, taken as a whole, very little difference was noted in the body weights of the experimental and control animals. The average weight of the former at the time of operation was slightly less than that of the controls, and when sacrificed from the fourth to the seventh week after operation, there was a slight gain in favor of the experimental animals, but both values are possibly within the normal limits of variation.

In regard to the growth of the genital organs, a much more noticeable increase took place in favor of the experimental animals. The total weight of the testes of these was 12,815 mg. against 9,950 mg. total for the controls.

It was noted, also, that the experimental guinea pigs showed a marked increase in the size of the seminal vesicles over those of the controls. No mention appears to have been made by other investigators concerning these organs. The experimental animals showed a total weight of the seminal vesicles of 11,450 mg. against the controls' 7,000 mg., or an average of 763.3 mg. for the former against 466.6 mg. for the latter.

Microscopically, the differences in the testes of the experimental and control animals were perhaps not so marked as might be expected from a comparison of their gross size and weight. Nevertheless, in this respect also, there were changes which indicate a hastened development of the organs under consideration. The most marked differences occurred in animals which were sacrificed between the ages of nine and eleven weeks. If sacrificed before this age, practically no microscopic differences could be detected, while later than eleven weeks the difference again became very slight owing to the proximity of normal maturity.

When taken during the age of maximum difference, the testes of the experimental animals showed relatively large tubules, their lumina being almost entirely filled with the many layers of spermatogenic cells in all stages of growth. Active spermatogenesis was evident. Interstitial cells were abundant, but could not be distinguished in size or in number from those of the controls. The tubules of the controls were definitely smaller, when exactly similar portions of the testes of each were studied, and the layers of spermatogenic cells in the lumina were fewer by far, than was the case with the experimental animals. Occasionally there were a few mature spermatozoa, but these were rare, and there was much less uniformity of development, portions of the testes showing tubules in a very immature stage without even a beginning spermatogenesis.

The microscopic picture in the seminal vesicles of the two sets of animals was far more striking than that of the testes. Here no particular age of maximum difference could be determined except that, earlier than eight weeks of age, the vesicle always appeared immature in the case of both. Beyond this age, there was a rapid change in the experimental animals, manifested by an enlargement of the lumen of the vesicles at the expense of the thickness of their walls. The cells of the lining mucous membrane were seen to increase in height, while in most cases there was an abundant secretion of colloid material completely filling the lumen.

Results in Females.—As regards results in the females, in accordance with the observations of other investigators, no differences could be made out in size or weight of the genital organs, nor was there a demonstrable difference when these tissues were studied under the microscope. As to body weight, it may be said that a similar curve was shown as in the case of males, excluding those which became pregnant, in which case, naturally, a normal rapid increase was evident.

As to physiological evidence of hastened maturity in the females, the incidence and termination of pregnancy was the only factor which could be reported, and the results were inconclusive, owing to the fact that in most cases the males were sacrificed before the age of full sexual maturity was reached.

Of the twenty females, in which total pineal extirpation was shown to have been accomplished, three became pregnant, while among the same number of controls there were but two. All three experimental guinea pigs were delivered of their young, ten days or more, before either of their controls, the earliest of the experimental being delivered three weeks before either control. When it is considered that the normal age for guinea pigs to reach sexual maturity is about nine weeks, it will be seen that, in the above instances at least, this period was shortened one-sixth to one-third.

A series of operations on young rats also was undertaken, and although an epidemic ruined nearly all of the experiments, it was immediately evi-

dent that, excluding such an unforeseen factor, these animals on the whole made the more ideal subjects for pineal experimentation. Litters are large and the interval between birth and sexual maturity is longer than in guinea pigs. The pineal gland itself is much shorter and less fragile, and can be picked out easily and surely with a pair of small forceps. Aside from the demonstration of the comparative ease of the operation, which indicates that this species is the most desirable for future studies, the results for immediate purposes were inconclusive.

Dandy's Experiments.—Dandy, in 1915, described a new and simple operative technic which obviates much of the trauma and consequently lessens the mortality.

The new operation can be done in less than one hour. It differs from earlier operations, in that the pineal is reached from in front through the third ventricle, rather than from behind. In this way the extensive bleeding consequent to liberation of the vein of Galen is obviated,—side-tracked as it were,—and the operation can be performed almost bloodlessly.

The method is to divide the splenium of the corpus callosum in the midline for a distance of about 2 cm. from its posterior terminus. This exposes the transparent roof of the third ventricle, which is distended by the contained cerebrospinal fluid. A large anemic area is visible in the midline of the roof of the ventricle, between the two small veins of Galen. This is perforated and the opening enlarged backward to the origin of the vena Galena magna by releasing the blades of the forceps. The entire third ventricle is thus brought in full view and under the origin of this vein, in the median quadrigeminal groove, the pineal body is readily seen. It can easily be grasped in the jaws of the cupped biting forceps and completely removed. The accompanying drawings by Broedel render any description of this operative procedure superfluous. (See original publication.)

Practically no bleeding occurs during the exposure of the gland. A little bleeding follows its removal, but this can easily be controlled by a minute tampon of cotton. With collapsed ventricles the bleeding is outward through the wound and is, therefore, not to be feared. Not infrequently, the aqueduct of Sylvius may be filled with blood. This has never caused any mortality because, before closure, the mold of clotted blood may be readily extracted, the aqueduct of Sylvius being in full view. To insure complete excision a second piece of tissue was invariably removed from the pineal region. With this method of operating there has been practically no mortality. It is however, quite easy to become disoriented, even when following carefully Dandy's procedures. If bleeding and laceration of tissue are avoided, as they can be, and the midline is adhered to, there is little danger of losing one's bearings.

Dandy made use of this method in removing the pineal gland from a series of dogs, mainly young puppies, from ten days to three weeks old. Of these one lived fifteen months after the operation; one died of distemper one year after operation; several survived the loss of the pineal three to eight months. Dandy was, however, unable to note any difference in the resistance of the operated and the control animals to the usual diseases.

When litters of puppies could be obtained, one or more of the animals were kept as controls. Little importance, however, should be attached to such comparisons because of the great variations found in members of the same family. The pineal was also removed in several adult male and female dogs, and three of these lived longer than four months after the operation.

Careful observations were made of the growth of the experimental animals. Skiagraphs were taken at various periods, but there was no evidence of either superior or inferior somatic development or adiposity, save perhaps in a single instance. In this animal there was slight increase in weight for a brief period, about one year after the operation. This gain, however, might be attributed to overfeeding. There was nothing in the behavior of the experimental animals to suggest mental precocity.

Dandy observed nothing to support the view that the pineal gland inhibits the sexual functions, and that its removal is followed by excessive sexual development. Two bitches lived for one year following the removal of the pineal; both were in rut ten months after the operation, or when about one year old. In neither animal did pregnancy result, and in neither was any abnormality observed in the generative organs.

The experimental young male puppies, observed for periods of from three to eight months, contrasted with other members of the same litter, gave no evidence of sexual precocity or retardation.

Dandy's experiments led him to the final conclusion that, so far as his work went to show, pineal extirpation gives rise to no sexual precocity, indolence, adiposity, nor emaciation and no somatic or mental precocity or retardation. No evidence was found that the pineal has an active endocrin function in either young or adult dogs. The organ is not essential to life and seems to have no influence upon the animal's well being.

From the literature as a whole, no final conclusions can be drawn. As a general principle in biologic experimentation, negative results in one species cannot be regarded as disproving positive results in another. They do, however, if performed with adequate technic, establish a sufficient degree of antecedent probability of error as to demand further studies. It is within the realms of possibility, that in some species the pineal retains a degree of functional capacity which has been lost in others. It is possible that in the dog the pineal function has been completely taken over by other organs. In such case, only negative results could be expected. It is to be hoped that further studies may soon be made in a variety of animals, and that the question may be settled beyond peradventure, as to whether pineal deficiency results in any characteristic changes in growth or development, and especially in the sexual sphere.

III

Chemistry of the Pineal Gland

Assaying Pineal Materials.—Because of the relative unimportance of the pineal gland in the endocrin congeries, but meager attention has been devoted to the development of methods for the quantitative assay of pineal

extracts. In the case of pituitary and adrenal extracts, elaborate and reasonably precise methods have been evolved for determining in terms of physiologic activity, the relative strength of various preparations. These quantitative standardization methods have been of immeasurable value for pituitary extracts for which no specific chemical tests have been devised, either qualitative or quantitative. The lack of similar tests for determining the strength of pineal extracts has hampered investigations directed toward ascertaining whether active principles of the pineal are confined to the glands of preadult animals, and whether heating and various forms of chemical manipulation destroy these principles. In fact, in case of any attempts at concentration and purification of pineal extracts involving fractioning, no means are accessible to indicate which fraction retains the active substances.

Technic.—The only attempt to quantitatively measure the strength of extracts from this gland has been made by McCord and Allen(*a*) in 1916. These writers point out that the action of pineal materials on pigmentation in tadpoles is a quantitative phenomenon which may be used as the basis for strength computation. In the feeding of pineal materials to the tadpoles, the time interval necessary to establish maximum contraction of the pigment cells increased as the concentration decreased. Tadpoles placed in a 1:500 pineal emulsion were noticeably lighter in five minutes, and required but thirty minutes to arrive at maximum translucency. In higher dilutions the maximum translucency was attained only after a longer interval and in very high dilutions producing only qualitative changes, the maximum was not attained. The dilution of 1:100,000 was the highest that produced a microscopically discernible qualitative action.

The quantitative relations between concentration and time will be evident from the following table:

Dilution of Acetone Extract	Maximum Reaction Attained in Minutes
1:500	30
1:1000	45
1:2000	60
1:5000	105
1:10,000	Qualitative change but maximum not attained.
1:100,000	Maximum not attained.

The maximum reaction was determined by comparison with a standard, consisting of several tadpoles which had been placed in a 1:500 pineal emulsion thirty minutes prior to the beginning of the experiment. The translucency thus obtained was found to be maximum. It served as the

criterion for comparison as to the degree of depigmentation induced by pineal preparations of unknown activity. In the practical standardization of pineal preparations, the end reaction accepted was the comparative time intervals necessary to attain to maximum translucency. With Bufo americana, pigment changes were found to be too trivial to be of value in standardization. Rana pipiens were exquisitely responsive and admirably suited for standardization purposes except that only during the spring months are they obtainable.

It was determined that the growth stimulating principle in the pineal is distinct from the principle concerned in pigment changes and this, on further investigation, more or less, may invalidate this proposed means of standardization.

Results.—Making use of this method of standardization, McCord and Allen sought to determine the relative activity of various split products derived from the pineal gland.

In the preparation of these split materials, the fresh glands were either ground up and immediately extracted or desiccated and subsequently extracted. After numerous observations with a variety of fractionation methods, it was found that chief interest centers around the acetone and alcohol extractives and their residues. In the case of acetone, the process was carried out in a Soxhlet apparatus. On freeing the extractive from acetone, there resulted a brownish black fatty mass with an odor suggestive of crude fish oil. Portions of these extractives and the residue were preserved intact for experimentation. Other portions of both were reëxtracted with alcohol. Likewise, fresh pineal material was extracted with alcohol, and the residue and extractives, respectively, extracted subsequently with acetone. These several preparations were tested, as to their influence upon pigmentation, on several hundred tadpoles from the same hatchings. At once it was apparent that the pigment altering principle was completely dissolved in acetone. The typical pigment cycle was induced by this extract, while the residue as well as all control acetone extracts of muscle tissues induced no pigment changes. The residue from acetone extraction was, however, capable of inducing the growth stimulating action described for the pineal gland, while the acetone extracts, which were exquisitely active in inducing pigment alterations, were only slightly active in stimulating growth. The inference is that at least two distinct principles exist in the pineal, the one producing the pigment phenomena, the other stimulating growth. In the case of the alcoholic extraction, the active substances were not readily soluble, for the alcoholic extractives, the alcoholic residue, and the acetone reëxtractives, all yielded positive pigment results.

WEIGHT OF GLANDS OF CATTLE, SHEEP AND LAMBS WITH LOSS OF MOISTURE AND PETROLEUM ETHER SOLUBLE SUBSTANCES

	Fresh Glands						Desiccated Fat Free Material									
	Total Number of Glands	Average Weight of Glands	Maximum Weight of Glands	Minimum Weight of Glands	Moisture in Fresh Glands	Petroleum Ether Soluble Substances	Yield of Desiccated Fat Free Material	Moisture	Ash	Phosphorus Pentoxid (P_2O_5)	Total Nitrogen	Protein (Nitrogen × 6.25)	Ash, (Dry Basis)	Phosphorous Pentoxid (P_2O_5), (Dry Basis)	Total Nitrogen, (Dry Basis)	Protein, (Dry Basis)
		Gm.	Gm.	Gm.	%	%	%	%	%	%	%	%	%	%	%	%
Pineal Glands from cattle. Collected March, 1915.	886	0.21	0.60	0.10	83.9	2.2	13.9	3.75	7.35	3.76	12.72	79.5	7.63	3.91	13.22	82.63
Pineal Glands from cattle. Collected Dec., 1915, and Jan., 1916.	1,458	0.18	0.35	0.09	81.6	2.8	15.6	5.10	8.10	3.75	12.68	78.94	8.53	3.95	13.31	83.19
Pineal Glands from sheep. Collected Dec., 1915, and Jan., 1916.	1,348	0.12	0.25	0.05	82.7	2.5	14.8	6.65	8.20	3.44	12.68	79.25	8.69	3.65	13.44	84.00
Pineal Glands from lambs. Collected Dec., 1915, and Jan., 1916.	5,062	0.08	0.18	0.04	83.5	2.5	14.0	6.25	7.05	3.16	12.83	80.19	7.52	3.37	13.69	85.56

Chemical Analysis of the Pineal Gland.—Data for a discussion of this topic are highly inadequate. By all odds the most complete analyses available were made by Fenger in 1916. For these analyses he collected approximately 900 glands from full grown cattle during March. Then during December and the following January of 1916, 1458 glands from cattle, 1348 glands from sheep and 5062 glands from lambs were obtained. All these glands were removed from the brains immediately after the heads were opened. The trimmed and cleansed glands were weighed and stored at freezing temperature until the entire lot had been collected. The various lots were finely minced and desiccated *in vaccuo,* at a temperature between 35° and 37°C. After drying to constant weight, the glands were coarsely ground and extracted with petroleum benzin in a Soxhlet apparatus. The weight of the fresh glands, together with the loss of moisture and petroleum ether soluble substances, may be found in the accompanying tabulation on page 253. On the desiccated fat free material, moisture, ash, phosphorous acid and total nitrogen were determined.

When these tabulations are compared, it will be noticed that cattle glands are relatively small, and that sheep and lambs contain much more pineal tissue per unit of body weight than cattle. The ash and phosphorus in the infant glands are somewhat less and the total nitrogen slightly higher than in adult glands. Pineal glands from lambs contain less phosphorus than sheep glands and these in turn less than cattle glands. All the samples were tested for epinephrin and iodin with negative results.

The Pineal: Some Pathological Considerations . . . . . .

. . . . . *Smith Ely Jelliffe*

Structural Considerations—Cysts—Pineal Sand—Hypertrophy—Tumors—Mixed and Compound Tumors—Functional Pathology of Pineal—Muscular Syndromes.

Pathological Considerations of the Pineal

SMITH ELY JELLIFFE

NEW YORK

At the present time a pure pineal-body pathology cannot be written. A large body of uncorrelated observations is obtainable but a satisfactory systematic mode of dealing with them is not yet possible. The best that can be done is first to summarize the various types of tissue involvements that have been reported, and, second, to present what general evidences of correlation there may be between changes in the histological structure in the pineal body and disturbances of the bodily condition.

The first series of observations may be regarded largely in the light of pathological museum collecting; the second offer some opportunities to determine possible rôles that the pineal body may play in the scheme of bodily organization, i. e., what in a general way may be said to be the pineal functions.

I. Minute consideration has been given to the histology of the pineal body which has in general demonstrated the possibility of its playing a dual rôle. It is a complex of organs rather than a single organ, the general features of which have been most exhaustively dealt with by Tilney and Warren (1919) and recently summarized by the writer (Jelliffe, 1920).

The phyletic, embryological, and histological evidence tends to show that:

[1] The pineal may be considered as a complex of organs of which the subcommissural body may be considered an essential part.

[2] That in this complex two separable structure types are present, one of which apparently is undergoing regressive and involutive subordination, the other a progressive evolution apparently related to developing functional capacity.

[3] That the former organs are possibly linked up with photic and thermic stimuli, and the latter with chemical regulators of metabolism, i. e., having an endocrin function.

[4] That the consideration of the pathology may in a general way be regarded as resulting (a) from changes in the pineal body itself, as various forms of diminished, increased, or disharmonic capacity, or (b) from the fact that new growths from the pineal structures by pressure

upon closely related brain structures will bring about neurological syndromes which may be associated with true pineal symptoms or may develop solely as symptom pictures of alterations of other anatomical pictures without any as yet known pure pineal correlations. These latter neurological syndromes are considered in the succeeding chapter.

Structural Considerations.—Defective pineal states are practically very rare. Two reports of apinealism are alone on record at the present time. Experimental removal of the pineal has been discussed elsewhere.

Zandréns (1921) has given a detailed analysis of an infantile symptom complex in a boy of 16½ years who was found to have no pineal. This case history will be discussed later. The significance of apinealism in certain animals, crocodiles, for instance, has as yet no explanation.

Hyperplastic states are better known. These may involve many or few of the tissue elements and are as a rule treated of as tumors of the pineal.

Cysts.—The cystic type of tumor was the first recorded even by the ancients. Virchow studied these and Marburg's (1908) monograph on the subject still presents the chief features known. He treats of them as: (1) Vascular scleroses or thromboses with resultant cystic involution. (2) Retention cysts lined with ependymal cells and resulting from complicated embryological anomalies or developmental anomalies. Nassetti (1912) has contributed a short study to cystic developments.

Pineal Sand.—This has been known from ancient times, and is more or less universally found. At one time thought of (Marburg, l. c.) as an inevitable sign of involution, Krabbe (1911) has demonstrated its presence in the very young and it may be absent in the old. Whether its presence is evidence of disease of the pineal is still a discussable question, but since the advent of the *x*-ray has offered an intra-vitam method for finding it (Schueller, 1909), the presence or absence of pineal sand will be more carefully correlated with clinical pictures. Drelincourt, Schnepf, and Boas and Scholz (1918) have reported very large concretions.

Inasmuch as sand concretions are not to be considered as necessary evidence of involution, it may turn out that the other assumed evidences bearing on the non-functioning of the pineal body, such as neuroglia proliferation, pigmentation, etc., will also be found faulty. In fact, Krabbe's and Schlesinger's (1917) studies on the pineal body in the aged seem to point to a continued functional activity—and since Achucarro's studies on neuroglia have shown this tissue to be a chemically functioning tissue and not a support substance alone, the pathological criteria of involution will have to be revised.

Hypertrophy.—Virchow discussed hypertrophy of the pineal which he observed in a child dying of measles with hemorrhagic engorgement

of the spinal cord, and also in an old woman in whom there was a complicating psammoma of the dura. Virchow has also collected a group of similar cases as reported by Meckel (1815), Oesterlen (1845), Lieutaud (1796), and Morgagni. As part of a general pluriglandular dystrophy in a myxedematous acromegalic, Heurot (1882) found a hyper-

Fig. 1. Photograph of patient with teratoma of pineal. Mild Fröhlich's syndrome. Cachexia, slight genital character precocity.

trophied pineal body. Legros (1873) has gathered many of the ancient reports of hypertrophy.

From the standpoint of the present day pathology these need careful differentiation, as some of the ancient observations would be classified as well differentiated tumor formations, and many other so-called hyperplasias are really not hyperplasias but atrophies with neuroglia placques, cysts and sandy concretions. They are enlarged pineal bodies, but not to be considered as hypertrophies of any functioning cellular elements. Marburg (1920) has accented this and Bell (1917) has comparatively recently gone over the question in adding two new cases to the literature.

Functional correlations have not been made with these hyperplasias which will as yet repay more extended analysis.

Tumors.—Tumor diagnosis offers particular difficulties since the definitive histological components in the pineal are still under discussion. Marburg preferred to speak of cysts, of teratomata, and all the rest he designated as mixed tumors, but following Horrax (1916) it seems justifiable to make a rough grouping of other tumor types, even though the pathological pictures are somewhat confusing or conflicting. Hence we may speak of gliomata with gliosarcomata, sarcomata, carcinomata, psammoma and mixed tumors.

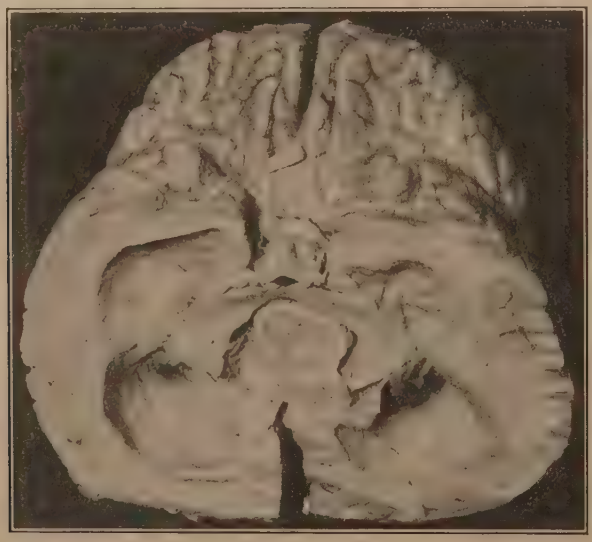


Fig. 2. Showing pineal tumor, teratoma, of patient in illustration preceding. Dilatation of ventricles, flattening of corpora quadrigemina. Hydrops of infundibulum to which adiposis genitalis is probably due from interference with hypophyseal reflex arc fibers.

Gliomata.—Feilchenfeld (1885), Reinhold (1886), Schultz (1886), Zenner (1892), Laurence (1899), Duffin (1876), Nothnagel (1888), Raymond and Claude (1910), Southard (1905), Marburg (1907), Neumann (1901), Verger (1907), Howell (1910, 3 cases), have described tumors of the pineal which they have arranged within the glioma or gliosarcoma group. They have no special bodily pathology as yet ascertainable.

Teratomata.—These constitute the most striking of the tumors of the pineal. Since Weigert's initial description, the discussions concerning their origin have opened up fascinating paths of pathological import which cannot be entered into here. They have been found mostly in the young, nearly all (Neumann excepted) having been observed before the fifteenth year. Wilms (1895) and Askanazy (1906) assumed they were related

to the pineal eye component of the pineal body complex to which general hypothesis Marburg (1907) gave his support, although Kidd (1913) without stating his reasons assumes it may be dismissed.

At all events, the teratomata have afforded the most interesting cases, neurologically speaking, although as yet no striking features in the clinical syndromy seem to set them off from other types of tumors, either as regards the metabolic disturbances, which might have been supposed to be present, or the neighborhood syndromes. This matter has not as yet been sufficiently analyzed in terms of increased or diminished functional capacity. The chief recorded cases of teratomata are those of Weigert, Gauderer, Coats, Falkson, Gutzeit, Neumann, Hueter, v. Frankl-Hochwart, Bailey and Jelliffe, Hymans, Takeya, Fukuo, Odermatt and Boehm. The pineal syndrome observed in most of these cases is considered elsewhere.

Carcinomata are recorded by Massot, Horrax, Forster, Daly, Hempel.

Mixed and Compound Tumors.—Other tumors have been described also: Ependymal Neuroglioma (Pappenheimer); Chorio-epithelioma (Askanazy); Adenomata (Meyer); Lipoma (Hertz); Sarcomata (most numerous), (Nothnagel, v. Hoesselin, Turner, Kwy, Ogle, König, M. Neumann, Oestreich Slawyk, Friedreich, Hart).

II. Functional Pathology of Pineal

Turning now from a more formal and statistical type of museum neurology, the functional pathology of the pineal claims attention. Here facts, speculations and dreams are still inextricably bound together. Laignel-Lavastine, in his masterly study on the Internal Secretions and Neurology (1919), has emphasized this necessity and the situation has not radically altered since then. Following the example set by this student of endocrinological problems, a graded series of observations passing from the more capable of substantiation in the present stage of our ignorance to those as yet only guessed at by adventurous speculations may be recorded.

In the clinical section attention has been called to the striking correlation between involvement of the pineal, in early years (chiefly teratomata), and altered activity of the gonadal system, resulting in an early development of the primary and secondary sex characters.

Pellizzi gave the impetus to the generalization of a relation of the pineal and macrogenitosomia and the experimental work inaugurated by Foà (1912) and Sarteschi (1910) in Pellizzi's clinic would tend to support the general hypothesis, even though there are many conflicting observations, attention to which has already been called in the physiological discussion.

This interrelationship hypothesis is that destruction of the pineal calls forth an over-compensatory hypertrophy of the gonadal systems, which results in the early sexual ripening of the vegetative, sensori-motor and symbolic sexual factors. Timme has described a series of resultant end-products in the vegetative field.

Since Pellizzi's (1910) cases are known practically only through abstracts of his original paper they are here reported more in detail; neither of the cases were autopsied. According to a personal communication from Pellizzi (1920) his first patient is still alive in South America.

Case 1.—[G. B.] A boy five years of age of healthy parents. Growth was normal in infancy. At seven months the penis began to enlarge and the body weight was above the average. The dentition was retarded, the first teeth appearing at fourteen months; speech was retarded slightly until about the twentieth month, when he commenced to use a few words. Erections were noted at the age of two and followed shortly by ejaculation. The body weight was above the average but the general mental development was not as robust as the physical development. Ejaculation occurred at night and also in the day time at weekly intervals; was not apparently induced by masturbation, and the semen contained "hemaspermi numerosi." The psychical development of the boy was retarded. He spoke many words badly, was capricious, bad tempered, vicious, and very irritable.

At his entrance into the clinic at Pisa he was four and a half years of age. His head was comparatively large, the body robust and strong, the skin was pink, the fat was ample, but not excessive, and muscular development was good. The bony development was in good proportion. The teeth were sound, twenty in number. The penis was large, the entire genital apparatus like that of an adult, and well covered with dark hair. The testicles were well developed. The axillary hair was also well developed. Radiographic study showed the ossification of an adult of from sixteen to nineteen years of age. The sella turcica was normal. The Binet Simon tests showed a psychological age of about four.

The diagnosis of pineal involvement was evidently made solely upon the hypothesis that the *macrogenitosomia precoce* was *per se* due to pineal disease as no symptoms referable to this organ were present in the history. No pineal shadow was demonstrable on the X-ray plate illustrating the head, which, as the author remarks, is not very good, as it was hard to keep the boy quiet.

Case II.—This history was taken from the notes of the clinic and not seen by the author:

A. R. had entered the clinic in 1901. He was then five years of age. The parents were healthy. He was normally born, being one of ten children. He had a severe enteritis as a baby and then had some slight convulsive movements limited to the ocular muscles at the age of six months. They then became general, but were not severe. When he was a year old he was somewhat rachitic and hydrocephalic. The head was large, with prominent frontal bosses. The mental development was slow. At about the age of two the penis and testicles began to increase in size, the body remaining proportionate to the age. The muscles of the arms were larger than normal, those of the leg were flaccid and hypotonic. Marked voracity was present.

At five the boy was markedly hydrocephalic, with large asymmetrical head.

The upper lip was hairy, also the pubis. The upper extremities were disproportionately large as compared to the lower. Abundant panniculus of chest and abdomen was present. There was no cranial nerve alteration. The erections were marked; the semen contained spermatozoa. The boy was good tempered and docile, affectionate to those who fed him. He spoke in monosyllables but was not capable of the simplest reasoning. He died from gastroenteritis in 1902, having been taken home in order to avoid an autopsy.

As may be seen, the belief that this patient had pineal disorder is also founded solely upon the precocious genital development. Pellizzi then develops his thesis, using the cases of Hudovernig and Popovits, Ogle, Oestrich and Slawzk, v. Frankl-Hochwart, Gutzeit, Parhon and Zalplachta, and only really raises the question of a possible reciprocal relation between hypopineal and hypergonadal function.

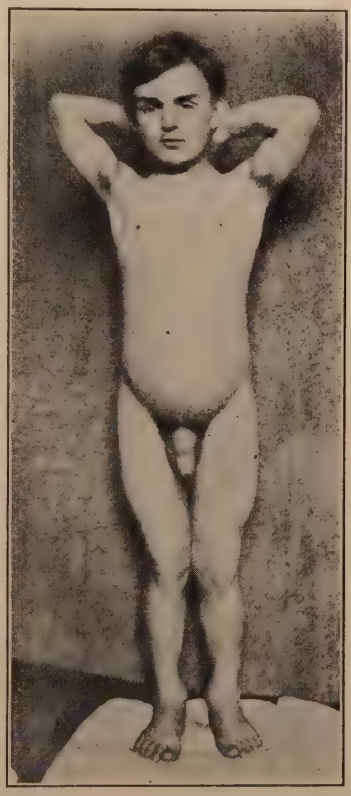


Fig. 3. Illustration of Pellizzi's case of Macrogenitosomia precoce from supposed pineal involvement.

Important contradictory facts are known in which early destruction of pineal substance has not produced the gonadal alterations, and second, sexual precocity of marked character has been observed without any known involvement of the pineal. This latter statement must be qualified by saying that the pineal has been found intact according to present day conceptions of intactness. When it is emphasized that no studies of the nerve mechanisms have been pursued in these studies, and furthermore when it must be confessed that the receptor and effector mechanisms in the pineal still remain unstudied, it is perhaps premature to say that the pineal is uninvolved. Pineal tumor cases without pubertas praecox are seen in the cases of Askanazy, Gauderer, Hart, Huter, König, Neumann, Pappenheimer, Fukuo and Schminck. All of the teratomata cases were in males varying from 4-27 years in age. There are at least 7 cases reported in adults and in at least two cases of teratoma (Huter and Pappenheimer) there was no sexual precocity observed.

It is a striking fact that all of the pineal teratomata which have been reported have occurred in males. In some of these teratomata of the pineal body there have been no signs of sexual precocity.

Zandréns (1920) has reported an extremely interesting case of apinealism. This was in a boy of 16¾ years who was infantile. He had

developed normally to the age of ten. He had not progressed much beyond that, and at practically 17 years of age was only 12, psychologically. The case was not one of Fröhlich infantilism, nor a gonadal infantilism. The subject was more of the hypothyroid type but showed no cretinoid nor marked myxedematous manifestations. The thyroid was apparently normal as was also the hypophysis. There was, however, marked hypoplasia of the testes and complete absence of the pineal. There was marked anemia. There was no marked intelligence defect.

Here then is a distinct contradiction of the Pellizzi hypothesis, and of the Marburg concept. If the pineal has a gonadal inhibitory effect, hypopinealism is supposed to result in gonadal precocity. Here, however, no such overcompensatory relationship is established. The Pellizzi-Marburg hypothesis has been reared chiefly on the basis (1) that tumor formation has resulted in hypopinealism and hence over-compensatory genital activity, and (2) conjectures concerning early involution of the pineal functions.

As will be here developed, this involution probably does not occur, and the pineal possibly has a group of other functions which must be investigated. The criteria adopted by earlier writers concerning involution are inadequate.

A modified hypothesis may therefore be introduced, namely, that tumor formation in the early stages is apt to induce hyperfunctioning of certain parts of the hormone activities of the pineal; these may accentuate gonadal function and lead to macrogenitosomia precox. Later destruction of the pineal will abrogate such function and cause the gonadal regressive functions already discussed. Jelliffe has called attention to the possible relation of the cachexia and anemia to heliotropic disturbances, and Zandréns has associated the anemia in his case with possible gonadal aplasia.

Complete fiber tract studies of Zandréns case have not yet been made, hence the neurological mechanisms are not further elucidated. Jelliffe maintains that these must be better understood before any generalizations will be valid. The time has passed when any strictly humoral hypothesis will explain the highly organized animal man. This organization is preeminently neurological, hence the problem is essentially to trace the efferent stimuli from the pineal depots, first through Cajal's receptor apparatus cells; then further learn what the connections are with other vegetative efferent stimuli, and finally through the tracts coming to and from the pineal work out the regulation mechanisms. As already stated (Jelliffe and White, 1919) the hormones are only a type of tool active at the metabolic level of the nervous system. They are servants, not masters, of the nervous system.

Boehm (1917) has recently collected the cases of pineal tumor presenting sexual precocity as follows:

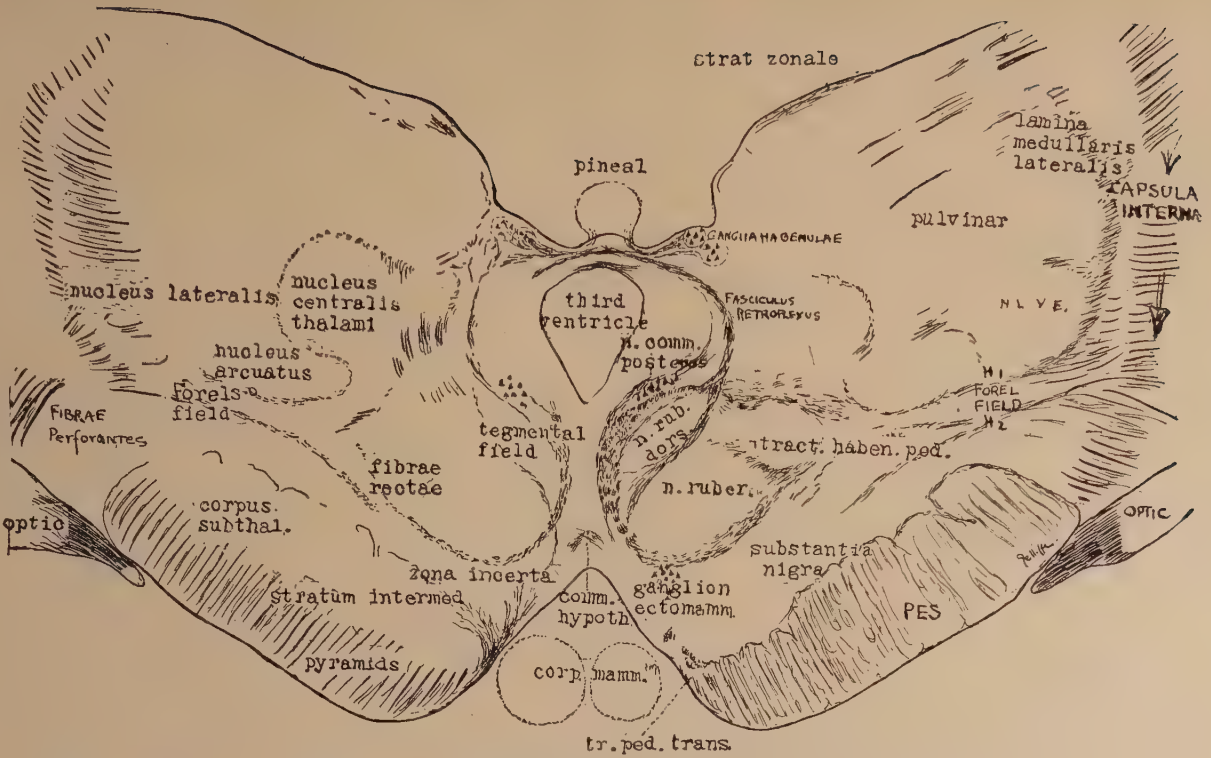


Fig. 4. Illustration of brain at level of pineal showing fiber connections with ganglia habenulae, relations of the fasciculus retroflexus with tractus habenulae pedis. Possible connections with substantia nigra, not yet elucidated.

1896 Gutzeit	Teratoma	7¾ yrs.	Early development of pubes.
1899 Oestreich	Psammosarcoma .	4 "	Abnormal development of penis. Genital hair.
1899 Ogle	Alveosarcoma ...	6 "	Early genital hair, and mental development.
1903 Holzhauer	Alveosarcoma ...	4 "	Genital development. Long bone development.
1909 Frankl-Hochwart	Teratoma	5½ "	Large development. Hairy. Genitals, + + Voice.
1910 Raymond and Claude	Glioma 10	"	Adiposis, hairy, mentally precocious.
1911 Bailey and Jelliffe	Teratoma 12	"	Adiposis, large, early mental development.
1913 Goldzieher	Angioblastosarcoma 16	"	Hair and genital development.
1913 Hijmans	Teratoma 8	"	Hair and genital development.
1913 Takeya	Teratoma 10	"	Hair and genital development.
1915 Odermatt	Teratoma 9	"	Hair and genital development.
1917 Boehm	Teratoma 9¼	"	Hair, genital, voice and mental precocity.

The cases of precocious puberty from gonadal tumors, that are markedly modified by simple removal of the tumors possibly remain outside of the just emphasized caution. Askanazy has stressed this point in his criticism of Marburg's generalization concerning the pathology of pineal tumors and sexual precocity, although leaning in part to support his argument on the old and we believe faulty deduction, which Berblinger also emphasizes, that the pineal reaches its maximum functional capacity at the age of seven. Krabbe's observations negative this view distinctly, and furthermore he has shown that between the eighth and fourteenth year a particular type of cell with basophil granules is a prominent feature of pineal histology, and secretory cells as described by Krabbe, Vigier, Uemura (1917), and Nicholas are found apparently functionally active at sixty (Uemura, Berblinger, v. Gierke, Schlesinger, Krabbe). Askanazy lays weight upon the ontogenetic nature of this early sexual precocity and since teratomata have given the chief evidences, speaks of the fetal factors involved in this early sexual maturity. Inasmuch as distinctly non-teratomatous and non-fetal pineal tumors are accompanied by the gonadal activities these still need an explanation not furnished by Askanazy's hypothesis. Furthermore the histological study of the gonads has almost been nil in these cases.

The final conclusion of the matter may be stated that for the present it may be assumed that Pellizzi's syndrome of macrogenitosomia may be related to increased rather than to diminished activity of the pineal gland.

As with the pituitary so also with the pineal, lipoid or pigment material is found in abundance. The fuchsinophil cells of Sarteschi are very pronounced and it may be that lipoid substances enter into the cycle of conversion products, not as waste pigment products, as has been

Fig. 5. Section at level of pineal and entrance of photic mechanism, chiefly of the eye proper, retinal and global associations. Pineal connections not certain.

so often inferred concerning lipoid substances, but as one of a series of conversion products in the elaboration and discharge of the definite chemical substances which serve as specific stimuli for the special receptors which entitles the pineal to be considered as an organ with a definite function or group of functions. Certainly the lipoid material related to the visual purple of higher photoreceptors, also found in parts of the pineal complex in other forms, must be considered more in the light of an active transforming material for light energies, rather than the inert substance it is usually viewed as being.

Muscular Syndromes.—Attention has been directed to the possible photic activities of the phyletically older components of the pineal complex. These may be assumed to have retained some phototropic functions. Such phototropisms are important in determining muscular adjustments. By what neuronic associations has not been worked out, but some evidence has been accumulated to show that a connection between the pineal complex and the metabolism of the phylectically older unstriped muscular tissue seems to exist. Thus in a group of muscular dystrophies the anisotropic disc portion of the compound muscle, which the researches of de Boer, Pekelharing, Pieron and others have tended to show are under vegetative nervous component control, is involved and peculiar muscular dystrophic syndromes have apparently resulted. Reference must be made to the work of Timme, Janney and Goodhardt, and others for more extended consideration.

Speculative investigation of atonic muscular states of the viscera (Hirschsprung's disease types, etc.), and their relation to pineal-adrenal dysharmonies are suggested in association with these observations.

Clinical Syndromes Involving the Pineal Gland.....

.....*Gilbert Horrax*

Introduction of Pertinent Data—Rarity and Incidence of Pineal Disease—Manifestations of Pineal Disease—General Pressure Symptoms—Neighborhood Symptoms—Constitutional Symptoms—Individual Manifestations—Bodily Overgrowth—Mental Precocity—Early Changes in the Primary and Secondary Sexual Characters—Adiposity, Polyuria, Polydipsia, Drowsiness—Diagnosis—Course and Prognosis.

Clinical Syndromes Involving the Pineal Gland

GILBERT HORRAX

BOSTON

Introduction

Paucity of Pertinent Data.—Our knowledge of the clinical symptomatology which is associated with disorders of the pineal body (epiphysis cerebri), has been built up from a study of about seventy-five case reports in which varying clinical symptoms have been associated with some definite pathology of the pineal as shown at autopsy. These meager data have accumulated during the past 120 years, starting with the record published by G. Blane in 1800. In almost every instance, the reports deal with tumors of the gland, the exceptions being two cases of hemorrhage described respectively by Simon and by Ziegler; one case of abscess by Birch-Hirschfeld (quoted by Marburg); and one case of syphilis by Lord. In one other case, reported by Pontopiddan, the author was unable to make an exact diagnosis as between syphilis and sarcoma.

Owing to the recent clinical studies by v. Frankl-Hochwart, by Marburg(*d*), and by Bailey and Jelliffe and to the experimental work of Foà (*c*), Sarteschi(*b*), Dandy, McCord(*a*), and Horrax, special significance attaches to the occurrence of pineal disease in individuals before the age of puberty. Of the cases recorded, twenty-three (or about one-third) have dealt with children under fifteen years of age, but only in eleven of these are there given sufficient clinical data upon which to base any conclusions. In addition to these authenticated cases, three others cited by Cushing, one reported by Morse, and two by the writer, have shown symptoms and signs of probable pineal involvement, but of course our knowledge here is purely speculative.

Rarity and Incidence of Pineal Disease.—It may be said, therefore, that disease of the epiphysis is very rare, and that the pathology is confined almost exclusively to tumors. Incidence of disease is twice as frequent in adults as in children, but it is only in cases which occur before the age of puberty that we see evidence of certain constitutional changes which it is thought may be connected with a disordered secretion of the pineal body itself.

Manifestations of Pineal Disease

The manifestations of pineal disease, then, may be grouped under three headings, as suggested by Marburg in 1913: (1) General pressure symptoms, (2) neighborhood signs, (3) constitutional symptoms. It is just possible that a fourth group should be added under which would come manifestations of multiglandular disturbance with the pineal playing the chief rôle, but for the present this last group is somewhat too vague to be included.

1. **General Pressure Symptoms.**—Little need be said as to this category since it includes all the usual and well recognized evidences of intracranial pressure characteristic of any brain tumor. Headache, of course, is very prominent and very severe because frequently due to internal hydrocephalus. The proximity of the pineal to the aqueduct of Sylvius causes any enlargement or tumor to obstruct the exit of cerebrospinal fluid with consequent backing up into the third and lateral ventricles. The headache is sometimes localized in the occipital or suboccipital region and may be associated with tenderness in this area. Vomiting, dizziness, bradycardia and generalized convulsions are other expressions of increased tension which occur in many cases. Choked disks are present in almost every instance, varying in degree from a slight edema with obscuration of the nasal borders, to a full-blown process giving an elevation of 5-6 diopters. This is usually an early finding and one which is rapidly progressive owing to the quickly developing hydrocephalus. The end stage of course will be a secondary optic atrophy, possibly with only a small residual elevation, and this may be the picture seen when the patient first comes under observation.

2. **Neighborhood Symptoms.**—This term was introduced by Cushing in classifying the symptoms of tumors involving the hypophysis. It refers to the special evidences of pressure on structures which lie in the region of a growth. As applied to the pineal, the principal structures concerned are (1) the corpora quadrigemina, (2) certain cerebral nerves, especially the trochlear and oculomotor, (3) the aqueduct of Sylvius, (4) the cerebellum and (5) the cerebral peduncles.

a. Involvement of Corpora Quadrigemina.—Perhaps the most significant of all the neighborhood symptomatology of pineal lesions is due to pressure upon the quadrigeminate bodies. They are usually the first of the nearby structures to suffer because of their very close proximity. The manifestations of such pressure are to be seen in pupillary changes. These are remarkable, not only for their diversity, but also for their extreme variability. In the same patient it may be noted at one time that the right pupil is larger than the left, while a few hours later, or perhaps the following day, the left pupil will be distinctly wider than its fellow. Permanent

bilateral pupillary dilatation has frequently been noted, together with a loss of reaction to light, even in the absence of any marked degree of optic nerve atrophy. Conjugate and skew deviations including the Majendie-Hertwig syndrome have been mentioned by Bailey and Jelliffe.

b. Involvement of Cerebral Nerves.—The third, fourth and sixth are the nerves most frequently disturbed, and practically every combination of eye muscle paralysis has been noted. With regard to the oculomotor, the superior recti seem to suffer most, while in many instances poor coordination of the ocular movements is observed. There is also sometimes ptosis of one or both upper lids.

Trochlear paralysis is of especial significance in tumors of the pineal, because this nerve is implicated more often than any other of the cranial series, and is frequently the first to be affected. The reason for this is easily seen from the anatomical position of the fourth nerve, curving out as it does just below the inferior colliculi over the dorsal surface of the midbrain. Isolated trochlear paralysis has been described by Gowers and Reinhold, while Nieden and Remak (quoted by Duret) have each recorded a case of bilateral involvement. Neumann states that the trochlear was involved in each of the five cases which he analyzed. Duret goes so far as to say that paralysis of the superior oblique in tumors of the pineal actually begins the "scene pathologique."

The abducens is also involved—at times along with the other eye muscle nerves, but sometimes alone as recorded by Nieden.

Facial paralysis has been described by a number of writers, including Neumann, Reinhold and Feilchenfeld. Deafness—either partial or complete—described by Falkson, Daly, Gowers and v. Frankl-Hochwart is no doubt due to pressure upon the auditory way stations in the median geniculates. Neumann also observed difficulty in swallowing, speaking and articulation. In a case recorded by Schultz, the patient could not swallow except when holding the head strongly forward.

c. Occlusion of the Aqueduct of Sylvius.—It is almost inevitable for epiphyseal growths to press upon the aqueduct of Sylvius, causing a damming back of cerebrospinal fluid and a consequent internal hydrocephalus (Fig. 1). This condition is noted in practically all the necropsy reports, and it is because of this fact, with its secondary effect upon the pituitary, that one must regard all statements relating to pineal adiposity with considerable hesitation. Indeed, in a recent unreported case of verified pineal tumor at the Peter Bent Brigham Hospital, radioscopy showed marked pressure changes in the sella, with destruction of the dorsum, and this finding is of course common in many cases of internal hydrocephalus. Marburg's theory, therefore, of a specific adiposity, attributable to an increased pineal secretion, will require much further evidence before its acceptance is justified. Polyuria, as related to pineal tumors, is also undoubtedly a secondary pituitary manifestation.

d. Symptoms Due to Pressure Upon the Cerebellum.—The symptoms recorded in some cases of pineal tumors have been so strikingly like those of a cerebellar growth as to make it seem probable that the lesion lay below the tentorium. Difficulty in walking, amounting even to "drunken gait" was recorded as early as 1837 by Schmidt and spoken of later by Duffin, Nothnagel(*b*), Howell, and others. It was present in the case at the Brigham Hospital previously referred to. Ataxia of the upper extremities, adiadochokinesia and positive Romberg's sign have been extremely frequent, while Kny and Feilchenfeld give instances of tremor of both hands and body. Oppenheim makes mention specially of vertical nystag-

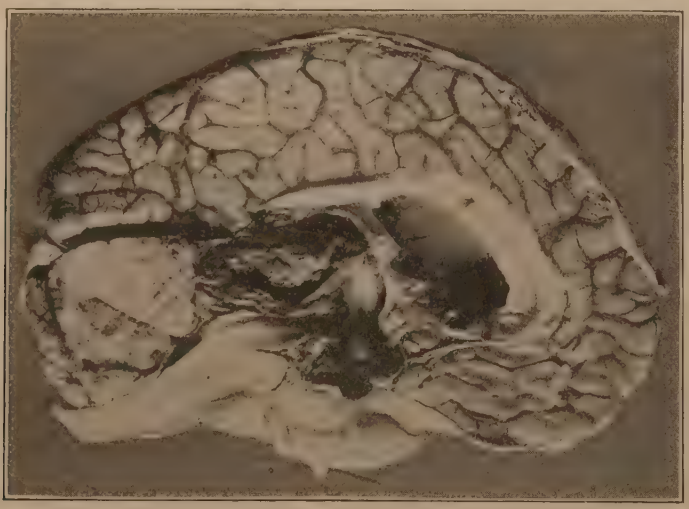


Fig. 1. Median section of brain showing tumor of the pineal region; also secondary ventricular dilatation. (Case reported by the author in 1916.) Reproduced by kind permission of the Archives of Internal Medicine.

mus, and lateral nystagmus has been recorded by Kny, v. Frankl-Hochwart, Bailey and Jelliffe and Oestreich and Slawyk. Many writers speak of retropulsive movements and opisthotonos.

e. Pressure on Cerebral Peduncles.—These structures are involved with great frequency, sometimes singly, but often bilaterally. Lord records a complete left hemiplegia with subsequent involvement of the right leg also, and Pontopiddan speaks of "left motor loss." Hyperactive knee and ankle jerks are noted by many authors including bilateral clonus by Schulz and Nothnagel(*b*). In a recent case, verified by autopsy, there was bilateral spasticity of both lower extremities, simulating experimental decerebrate rigidity. Athetoid movements are described by Lawrence so that in this case, the lesion had probably extended to the basal ganglia.

3. Constitutional Symptoms.—*Etiological Considerations.*—The foregoing recitation of the clinical symptomatology of epiphyseal disease ap-

plies to all cases alike, no matter what the age of onset. We now come to that special class of symptoms which may be called constitutional or metabolic, which are supposed to be related to a disturbed secretion of the cellular elements of the pineal itself. These symptoms occur only in children before the age of puberty. The question as to whether they represent an over- or an underactivity of secretion has been discussed by numerous writers. Those who believe that the changes are due to overfunctioning, base their ideas on the fact that sometimes, in other conditions, tumor cells elsewhere in the body have been found to take on and elaborate the function of the organ involved. These writers also point to the fact that certain investigators have produced a hastened maturity and physical growth, by feeding pineal gland substance to animals (Dana and Berkeley, McCord(*a*)).

On the other hand, there is considerable evidence that the constitutional manifestations of hastened maturity in children with pineal disease is due to underactivity. First, it is known that normally at the age of puberty the pineal undergoes atrophy. Second, in the reported cases of children showing the so-called pineal syndrome, tumors replacing the pineal were found at autopsy. Third, experimental extirpation of the pineal in young animals has been shown by some investigators to hasten sexual maturity (Foà(*c*), Sarteschi(*b*), Horrax). Dandy, however, in a series of experiments upon young dogs was unable to detect any constitutional manifestations.

Whatever the status of secretory activity of the pineal cells or whether they have any activity at all, we know from the case reports, in which data on this subject are included, that a fairly definite clinical syndrome occurs in children prior to the age of puberty, in whom at postmortem examination a tumor of the pineal has been disclosed. This syndrome has been given the name "macrogenitosomia-precox," and consists for the most part in a greatly hastened maturity both of body and mind, with an especially early and pronounced activity in the realm of both primary and secondary sex characteristics. The individual manifestations may be taken up further in detail.

Individual Manifestations

Bodily Overgrowth.—A general and rapid growth of the whole bodily frame is one of the most usual and evident findings in the clinical picture. Oestreich and Slawyk mention that their patient when four years old measured 3 feet 6½ inches, which is almost 6¼ inches more than ideal height for the age. V. Frankl-Hochwart's patient measured 4 feet ½ inch at the age of 5½ years, a height which one would expect of a boy of nine. In the case reported by Raymond and Claude, the subject at ten

years was 4 feet 6½ inches tall, i.e., corresponding to a boy of thirteen or fourteen years. An individual reported by the writer was 5 feet 3 inches in height at the age of twelve, which is seven inches above normal for that age.

Similarly in the matter of body weight, the patient of Oestreich and Slawyk was 20 kilos, or 4 over the normal; Raymond and Claude's subject was 39 kilos, or 13 above normal; and the writer's was 114 lbs., or 32 above normal.

Fig. 2. Case of teratoma of pineal gland (authenticated by necropsy).
Age—3 years.
Height—41.5 inches.
Weight—36 lbs.

Mental Precocity.—An advanced and more mature mental attitude, than would be expected for their age, has been mentioned specifically in several instances of authenticated cases of pineal tumor. This maturity of mind has varied from a simple heightened intelligence to a really extraordinary degree of mental attainment. Thus v. Frankl-Hochwart says of his patient, who at the time was five years old: "He spent much time in discussing the immortality of the soul, and the life after death." He adds that these ideas and subjects were not suggested to him by his relatives or friends. Raymond and Claude say that their patient, a boy of ten, "answers questions well, perhaps slightly better than most boys of his age." In the writer's reported case, it was mentioned that during the year of his illness, between the ages of eleven and twelve, "his mental development had been very noticeable, as exemplified by a more mature mental attitude, greater thoughtfulness, etc." These facts were vouchsafed by the child's parents, and were related before the diagnosis of pineal tumor was known.

In a further recently verified case seen at the Peter Bent Brigham Hospital (Fig. 2), it was noted in the history that the patient, a child of three years, "responds to questions rather more intelligently than might be expected of him."

Early Changes in the Primary and Secondary Sexual Characters.—Ogle, in 1899, was one of the first to call attention to changes in the exter-

nal genitalia. In a boy six years old, shown at autopsy to have a pineal teratoma, it was noted that the penis was fully equal in size to that of a boy of sixteen or seventeen and pubic hair was plentiful, but the testicles did not seem enlarged. Oestreich and Slawyk, also in 1899, say of their patient, who was four years old, that his penis developed enormously. was 9 cm. in length when flaccid, and his testicles were as large as pigeons' eggs. There was also abundance of pubic hair 1 cm. long. Frankl-Hochwart in 1909 says of his verified case in a boy of five that he showed great development of the penis, strong erections, marked growth of pubic hair and deep voice. Raymond and Claude noted that in their case, a boy of ten had pubic hair equal to that of a boy of fourteen or fifteen. In the writer's reported case, of a boy of twelve years, it was noted that the external genitalia were overdeveloped for the age of the patient, that pubic and axillary hair were present, and that the boy's voice changed from prepubertal to adult tone between the years of eleven and twelve.

Other secondary sexual features mentioned are mammary hypertrophy with colostrum present in a boy of 4 (Oestreich and Slawyk), early sexual instinct, masturbation and priapism.

Adiposity, Polyuria, Polydipsia, Drowsiness.—These are further manifestations of constitutional disorder to which attention has been called by various writers. Marburg, especially, has emphasized the importance of adiposity and went so far as to associate it with an oversecretion of the pineal. In view of the fact that these are all symptoms which are now pretty definitely shown to be dependent upon pituitary disturbance, their specific connection with the pineal can hardly be maintained. This seems the more true because secondary pituitary manifestations, together with marked changes in the sella turcica, occur with great frequency in cases of internal hydrocephalus from any other cause. Pineal tumors almost inevitably impinge upon the Sylvian aqueduct, so that dilatation of the third and lateral ventricles has been present in almost all of the recorded cases.

Diagnosis

The correct localization of pineal tumors has been accomplished antemortem only rarely. In adults no pathognomonic syndrome can be named, but in most instances the cerebellar symptomatology causes the greatest confusion. The most that can be said is that in the presence of an intracranial pressure syndrome which simulates a cerebellar lesion, if there be added to the picture an involvement of one or both trochlear nerves, together with recurring changes in the size of one or both pupils, and a tendency to spasticity in the lower extremities, a tumor of the pineal body should at least be suspected.

In children before the age of puberty, however, the case is different.

Here we have not only the indications of general intracranial pressure, but there may be added to this any or all of the constitutional manifestations. No better summing up can be given than that recorded in 1909 by Frankl-Hochwart, who says: "When one finds in a very young individual, along with the general symptoms of tumor, as well as the local signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor."

Course and Prognosis

Tumors of the pineal, up to the present time, have been inevitably fatal, whether or not a correct diagnosis has been made, and in spite of any therapy. The only chance in future lies in the possibility of making a correct diagnosis more often, so that in the light of greater familiarity with cerebral surgery, an approach to the pineal region may perhaps be worked out. No medicinal measures have been of any avail, except when, as was the case in one instance, the lesion was due to lues.

SECTION II

The Suprarenal Glands, Including the Chromaffin System and the Interrenal System, the Carotid and Coccygeal Bodies, and their Diseases

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Anatomy, Embryology, Comparative Anatomy, and Histology of the Suprarenals . . . . . *E. V. Cowdry*

Anatomy—Gross Morphology and Relations—Accessory Suprarenals—Embryology—Origin of the Cortex—Origin of the Medulla—Differentiation of Cortex—The Paraganglia—Variations in the Suprarenals under Different Conditions—Comparative Anatomy—Duality of Suprarenals—Conditions in Various Phyla—Quantitative Relations—Constancy of Cell Types—Histology—The Cortex—The Medulla—The Carotid Bodies—Anatomy—Gross Morphology and Relations—Embryology and Phylogeny—Histology—Cell Types—The Coccygeal Bodies. [From the Anatomical Laboratory, Peking Union Medical College.]

Chemistry of the Suprarenal Glands

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Historical

The study of the chemistry of the organs of the body is important, not merely as a question of scientific biochemistry, but because it may lead to the isolation of chemical compounds which nature, in the struggle for existence, has found useful in maintaining the functions of the body and protecting it against disease. From this point of view the study of the suprarenal, the pituitary and the thyroid glands seems at present especially important.

The work on the chemistry of the suprarenal glands may be divided into two periods—that done preceding the work of Oliver and Schaefer in 1894 and that done subsequent to it.

Earlier Work.—In 1856, Colin found that the application of ferric sulphate to the cut surface of the suprarenal glands produced a bluish color and, as this reaction was confined to the medulla, he argued that the medulla and cortex differed in composition. In the same year, Vulpian(*a*) reported that scrapings from the medulla of these glands reacted with ferric chlorid and other ferric salts with the production of a green or bluish-green color, but that at times the color was blackish, and that an aqueous solution of iodin, or of other oxidizing agents, produced a rose-carmine color. These reactions, he claimed, were peculiar to the suprarenal medulla and were given by no other organ. From a suprarenal vein and also from the vena cava just above the opening of the former, he obtained an iron-chlorid reaction and argued that these glands secreted into the blood.

In 1865, Henle pointed out that the most striking difference between the cells of the cortex and those of the medulla was that these medullary cells stained a dark brown color with potassium chromate solutions, whereas those of the cortex were almost unchanged by them. Later, Manasse(*a*) found that the suprarenal vein contained a hyaline substance, which stained with chromic acid like the suprarenal medulla.

Vulpian(*b*)(*c*) believed that the suprarenals of the python gave the

iodin, but not the iron reaction. However, he was inclined to believe that both reactions were probably due to the same chromogen, although he did not isolate it. As it was soluble in alcohol, he concluded that it was not a protein.

These color reactions of Vulpian were confirmed by Harley(*a*) and by Virchow(*a*). The latter believed that the chromogen was confined to the intercellular substance and did not occur in the medullary cells.

During the period between the appearance of Vulpian's report and that of Oliver and Schaefer the propulsive ideas in the study of the chemistry of the suprarenal glands became the isolation and identification of the chromogenic substance, or its color products, and of the toxic compounds; although some attention was directed to other constituents, inosit and large amounts of potassium were proved to be present (Marino-Zuco, Kulz). Cloez and Vulpian stated that the suprarenal glands contained alkaline phosphates and sodium chlorid and thought that taurocholic and hippuric acids were present in these organs, and that the first would break down into choloidic acid and taurin. After treatment with HCl, Seligsohn obtained crystals which he believed to be taurin. He stated that the glands contained Ca, Fe, Mg and benzoic acid. However, the work of Stadelmann(*a*) showed that the suprarenal glands did not contain hippuric, benzoic or the biliary acids (Beier).

A number of workers, Holm, Arnold(*b*), Krukenberg, Brunner, undertook to isolate the chromogen, or its derivatives.

Holm macerated suprarenal glands with alcohol and, after filtering, evaporated the alcohol, then precipitated the residue with a solution of neutral lead acetate. The filtrate was precipitated with lead subacetate, then with copper acetate and finally heated. The heavy metals were removed from the filtrate by H_2S. On concentrating, a violet-colored substance separated. This substance went into solution with acids. Holm pointed out that, on adding ammonia to an acid extract of the glands, the pigment separated in violet flakes; hence it was a base, but he did not have enough material for further study. He said that these organs contained a chromogen which, on oxidation, passed into a coloring matter.

Krukenberg inferred that the compound which gave the iron reaction was different from the one which reddened on oxidation. He based this partly on Vulpian's experiments with the suprarenal glands of the python and partly on his own observation that after long boiling in an open vessel, aqueous extracts of the suprarenals gradually lost their capacity to react with ferric salts. He believed that the red pigment was not always the same, because after obtaining the maximal red color with iodin, silver still gave another color (purple).

Krukenberg repeated Arnold's method, i. e., the suprarenals were digested with alcohol on the water bath, then ammonia and neutral lead acetate were added to the filtrate. The lead precipitate was extracted

with alcohol and ether, then treated with H_2O until the silver test for chlorids became negative. The precipitate was suspended in alcohol and precipitated with oxalic acid. The excess of oxalic acid was removed as ammonium oxalate. The red brown filtrate was evaporated to dryness, dissolved in absolute alcohol an dallowed to evaporate in desiccators. He suspected that his final product was a mixture of unchanged chromogen with decomposition products of it. His analyses gave 40.83 per cent C, 9.1 per cent H and 9.31 per cent N. This product contained Fe, but no S. Krukenberg did not attempt to construct a formula, but from his figures Moore calculated the empirical formula $C_5H_{14}NO_4$.

Krukenberg pointed out that the color reactions of the medulla were similar in many respects to those of pyrocatechol. This was confirmed by Brunner, who also showed that these extracts reduced Fehling's solution. From this time, workers became convinced of the presence of a pyrocatechol compound in these organs.

Later Work.—In 1894, Oliver and Schaefer(*b*) reported that extracts of the suprarenal glands, when injected intravenously into animals, caused a marked, transitory rise in the systemic blood pressure. These reports were followed by independent observations of Szymonowicz, and of Cybulski.

The striking effects on blood pressure and the successful clinical use of suprarenal extracts as a local vasoconstrictor soon excited determined efforts to isolate the compound which exerts this action and, as Bradford says, the history of the attempts to isolate and synthesize this compound forms one of the most striking and interesting chapters in the history of biochemistry.

Oliver and Schaefer(*c*) found that the pressor activity was confined to the medulla and made some attempts to determine the nature of the compound which produced it. They found that this compound was insoluble in absolute alcohol and ether, that alkalies injure or destroy it, that it dialyzes and is not destroyed by gastric juice, and stated that this compound is apparently identical with Vulpian's chromogen. However the chemical work was delegated to Moore, who was then working in Schaefer's laboratory.

Mühlmann claimed that after treatment of suprarenal extracts with HCl, a compound giving pyrocatechol reactions could be extracted by ether, but he did not isolate it. He believed that pyrocatechol existed in the medulla in a complex form. This work was not corroborated by that of Gürber or by that of von Fürth.

Fraenkel extracted suprarenal glands with alcohol or water and, after concentrating, extracted with boiling absolute alcohol. This extract was then precipitated with acetone and finally with ether. He obtained a syrupy residue which, on insufficient evidence, he regarded as pure. This he called sphygmogenin and believed it to be a nitrogenous pyrocatechol

derivative. He attempted to benzoylate it from a pyridin solution with benzoyl chlorid. However, Moore found that boiling alcohol soon destroys the pressor activity, but not its ability to respond to iron salts.

Moore(*a*) showed that the solubilities of the pressor compound were those of Vulpian's reducing body, but stated it did not reduce Fehling's solution. In later papers he argued that the pressor compound was not a pyrocatechol derivative, nor identical with the chromogen, partly because old alcoholic extracts of suprarenal glands gave no pressor response, yet gave the chromogen reactions (Moore(*b*); Moore and Purinton). However, he stated that this might mean that the compound which raises the blood pressure breaks into simpler ones, which also yield these color reactions, but which have no pressor activity, and that the pyrocatechol nucleus may have no direct connection with such activity. This may be the explanation of Elliott's(*b*) experiments.

Moore's main arguments were that simple pyrocatechol derivatives do not raise the blood pressure (compare also Velich(*a*)), that his study of Krukenberg's analyses suggested a pyridin derivative, while piperidin, a reduced pyridin, exerts a pressor action (Tunnicliffe) and that on fusing an extract of the suprarenals with KOH he obtained a pyridin odor.

In this country the chemical work on the pressor compound of the suprarenal gland was begun by Professor John J. Abel (Abel and Crawford). He treated an acid extract with benzoyl chlorid and sodium hydrate by the Baumann-Schotten method, then decomposed the product with sulphuric and glacial acetic acids. The resulting impure mixtures were physiologically active; the very active preparations gave both of Vulpian's color reactions, while the less active reacted only with iron.

Later he decomposed the benzoyl product by heating under pressure in the autoclave with water or dilute H_2SO_4. After removing benzoic acid, the solution gave a heavy precipitate with NH_4OH. On drying this with absolute alcohol and ether he obtained a grayish powder, which was almost insoluble in water, but which was soluble in dilute acids.

Abel calculated an empirical formula $C_{17}H_5NO_4$ for this base and $C_{17}H_{14}NO_4.COC_6H_5$ for the benzoyl compound. He named the product epinephrin or alkaloidal epinephrin.

Abel(*a*)(*c*)(*d*)(*h*) found that the base, obtained by precipitation with NH_4OH, gave the iron, but not the iodin reaction, was precipitated by alkaloidal reagents, but possessed very slight physiological activity. However, he noted that physiological activity persisted in those preparations which gave the iodin reaction. This inactivity and response to alkaloidal reagents might have been partly due to incomplete saponification of the benzoyl product or to chemical changes produced by the severe (autoclave) treatment or to the action of acids.

When the benzoyl product was heated in an autoclave with dilute H_2SO_4, a solution was obtained in which more complete saponification

of the benzoyl product presumably had occurred. This solution gave the iodin reaction and yielded a precipitate with picric acid which was physiologically active. In a dog (6.8 kgm.) with cut vagi, the intravenous injection of 0.0011 g. of this impure picric acid precipitate cause a rise in blood pressure of 46 mm. Hg, while 0.0042 g. produced a rise of 88 mm. Hg.

Using Abel's method, von Fürth could not obtain a physiologically active picrate and there may be some question whether Abel's precipitate might not have been a picrate of a modified epinephrin to which was absorbed some unchanged active compound; but, however this may be. Abel(*b*), from this precipitate, obtained very active preparations, i. e., sulphate $(C_{17}H_{15}NO_4)_2H_2SO_4$, an impure bisulphate, etc. The bisulphate (0.00013 g.) raised the blood pressure of a dog with cut vagi 14 mm. Hg, while 0.00043 g. raised it 60 mm. This activity would correspond to 0.000019 g. of the salt per kilo or to 0.000013 g. of free base. A sulphate made from the bisulphate was tested by Reid Hunt(*c*), who found that 0.083 millionths of a gram per kilo body weight raised the blood pressure of an atropinized dog 5 mm. Hg, while 5.7 millionths of a gram per kilo raised it 66 mm.

Abel did not obtain the active compound in the form of a free base, because, as is well known, the autoclave treatment destroys much of the active compound and NH_4OH will not precipitate it save from concentrated solutions.

Abel called his active product epinephrin hydrate or native epinephrin. In connection with the subject of two possible forms of epinephrin it may be remembered that Halle suggested that in the suprarenals there might be a series of closely related compounds.

Abel(*d*) made a mistake in naming the inactive product epinephrin and the active form epinephrin hydrate. If he had named his active preparation epinephrin and his inactive form epinephrin anhydrid much confusion would have been avoided, as anhydrids are often inactive. Further confusion resulted from his early failure to reduce Fehling's solution with his active preparations, but the physiological tests made by Hunt and by himself showed that he had a product with marked physiological activity. (Compare Abel and Macht.)

As one of its decomposition products Abel(*g*)(*k*) obtained pyrrol and at first believed the pressor compound to contain this nucleus. Abel's method was too involved and required the use of too expensive chemicals for commercial purposes, but Takamine soon isolated the pressor compound in a form which was commercially feasible.

Von Fürth(*a*), at first, used a method somewhat like that of Holm, i.e., he extracted with alcohol at low temperature, removed inactive substances with Pb acetate and precipitated the filtrate with Pb acetate and NH_4OH. This precipitate was decomposed with H_2S, evaporated in an

atmosphere of CO_2, and finally extracted with alcohol and precipitated with ether. From 2000 pig suprarenals he obtained about 0.4 g. of a nitrogenous compound, but he did not feel sure of its purity.

From a study of an impure acetyl product von Fürth at first argued that the pressor compound was either tetra-hydro-dihydroxy-pyridin ($C_5H_7NO_2$) or di-hydro-dihydroxy-pyridin ($C_5H_7NO_2$), but he soon abandoned this view.

Von Fürth(*a*) then started out from Hofmeister's observation that the chromogen is very resistant to reduction with zinc dust in acid solution. He extracted the glands with a dilute solution of $ZnSO_4$, removed heat-coagulable proteins, precipitated with NH_4OH, and then purified by an elaborate method. However, it is difficult to see how all zinc would be removed by this method. From 200 beef glands he obtained 0.5 g. of material. The intravenous injection of 0.00005 g. of this preparation raised the blood pressure of a rabbit 74 mm. Hg.

Later he extracted with acidulated water in the presence of zinc dust, concentrated, extracted with methyl alcohol, then removed some inert materials with $ZnCl_2$ and acetone, precipitated with $FeCl_3$ and ammonia, but his purified product was not uniform in composition. He named the pressor compound, suprarenin, although he only obtained it as his iron suprarenin compound. Of this iron compound, 0.000075 g. raised the blood pressure 24 mm. Hg in a rabbit weighing 2 kilograms. In a dog (6 kilo.) the intravenous injection of 0.0001 g. caused a rise of 4.6 mm. Hg. Five millionths of a gram of this iron compound, which equals about four millionths of a gram of free suprarenin, raised the blood pressure of a dog (7 kilo.) 14 mm. Hg (von Fürth(*b*)). Von Fürth estimated the glands to contain from 0.1 to 0.17 per cent suprarenin (Imray(*a*)).

After the papers of Takamine and Aldrich had appeared, von Fürth(*c*) (*d*) decomposed his iron compound with H_2S and heated the solution with NH_4OH and thus obtained a product which corresponded to that of Aldrich. He admitted that his iron method was likely to be attended with oxidation (Radziejewski).

Takamine extracted the glands with water, or acidulated water, covering the surface with fat to lessen oxidation, coagulated the proteins by heat, then concentrated *in vacuo* and precipitated with NH_4OH or NaOH. This crude product was then dissolved in acid and precipitated with alcohol and ether. On reprecipitation, it appeared as a white, microcrystalline substance, which yielded five different crystal forms. This substance, which he named adrenalin, produces a slightly bitter taste and reacts alkaline. To neutralize 100 parts of adrenalin required 27.38 parts H_2SO_4 or 19 parts HCl. It is soluble with difficulty in cold water.

Takamine pointed out that colorless solutions of adrenalin readily

oxidize, becoming pink and finally brown, that it gives the characteristic $FeCl_3$ and I reactions of Vulpian, energetically reduces gold chlorid, and is not precipitated by the usual alkaloidal reagents.

The secret of the isolation is the precipitation of the base by NH_4OH from a concentrated solution. Most workers, on account of expense of materials, worked with too dilute solutions.

Takamine's(*a*)(*b*)(*c*) analyses showed it to have 59.38 per cent C; 7.84 per cent H; 7.88 per cent N and 24.90 per cent O, and he calculated the empirical formula to be $C_{10}H_{15}NO_3$, but this formula has not been confirmed by others. Takamine showed that, in a dog weighing 15.5 kgm. 0.000016 g. of his product raised the blood pressure 9 mm. and that 1 c.c. of a 0.001 per cent solution raised the blood pressure 30 mm. Hg in another dog (8 kgm.).

Note. For data as to the pressor activity of various preparations see Crawford, 1907. (Crawford, A. C. Use of suprarenal glands in the physiological testing of drug plants. Bur. Plant Indust.)

Takamine secured patents covering the base, its salts and solutions. His rights were purchased by American pharmaceutical interests. Abel(*f*) has analyzed commercial adrenalin and found it to contain considerable amounts of phosphates.

Almost simultaneously with Takamine, Aldrich published his report. He was then engaged in commercial pharmaceutical research, but previous to this affiliation had been Abel's associate at the Johns Hopkins Medical School. Aldrich extracted the glands with a weak acetic acid solution, coagulated by heat, evaporated *in vacuo* and removed phosphates, etc., by lead acetate. After removing Pb, the filtrate was concentrated *in vacuo,* precipitated with alcohol and finally with NH_4OH. Aldrich's analyses showed C 58.03 per cent; H 7.20 per cent; N 7.66 per cent; O 27.11 per cent and the empirical formula was calculated to be $C_9H_{13}NO_3$.

Aldrich(*b*)(*c*) says that a purified preparation made from Takamine's product also gave C 58.03 per cent; H 7.20 per cent; N 7.66 per cent; O 27.11 per cent and that Takamine's adrenalin was identical with his. However, Aldrich does not state how he purified it, presumably he used Pb acetate. No doubt if he had purified Abel's active products in a suitable way he would have obtained similar results. Von Fürth's iron compound, on purification, yielded a compound giving the same analytical data, and Jowett states that the German products suprarenin, adrenalin and epinephrin all refer to the same substance for which he uses the term epinephrin.

Several other methods have been used for isolating this compound. Abel's(*j*) later method depends on the solubility of adrenalin oxalate in alcohol and was tried by Pauly, also by Abderhalden and Bergell. He extracted the minced glands with an alcoholic solution of trichloracetic

acid and after concentrating *in vacuo,* precipitated with NH_4OH. When washed with absolute alcohol and ether and dried *in vacuo,* it is an almost white powder.

Bertrand(*b*) extracted horse suprarenal glands with alcohol containing oxalic acid, shook out the concentrated filtrate with petroleum ether, precipitated with lead acetate and with NH_4OH as by the method of Aldrich. From 118 kgm. he obtained about 125 g. of adrenalin.

In Battelli's(*b*) method, which is a modification of that of Aldrich, the medullary substance is mechanically freed from cortex, then extracted. The extract is coagulated by heat, precipitated by lead acetate and the filtrate is freed from lead by H_2S, but $HgCl_2$ precipitation is used before the base is thrown out with NH_4OH (Ciaccio(*b*)).

Weidlein uses whale suprarenal glands.* To 1000 gm. of the disintegrated glands a solution containing 500 c.c. of absolute alcohol, 50 c.c. of chloroform and 25 c.c. of acetic acid is gradually added while shaking and the whole is let stand over night. The liquid is then pressed, made acid with 25 c.c. acetic acid (50 per cent) and coagulated on the water bath. The filtrate, which measures 600 c.c., is evaporated *in vacuo* to 60 c.c. and, after filtering, is precipitated with NH_4OH. The precipitate is dried with absolute alcohol and ether. The residue yields a further amount by using methyl alcohol in place of the ethyl alcohol. The product so obtained is purified by adding 20 c.c. of a 25 per cent solution of acetic acid containing 1 c.c. of sodium sulphite to 2.0525 g. of the impure compound then reprecipitating and drying as before. The suprarenal gland of whales weighs from 264 to 684 gm. and yield about 0.15 per cent of the pressor substance.

To avoid oxidation, Freund utilizes an electrolytic method for the reduction of impurities. He uses a platinum cathode, a carbon anode and a porous cell as a diaphragm. This patented method is claimed to yield a white "analytically pure" compound.

The percentage formula of Aldrich has been confirmed by Bertrand(*b*), Jowett, Pauly, von Fürth(*d*), Abderhalden and Bergell(*a*).

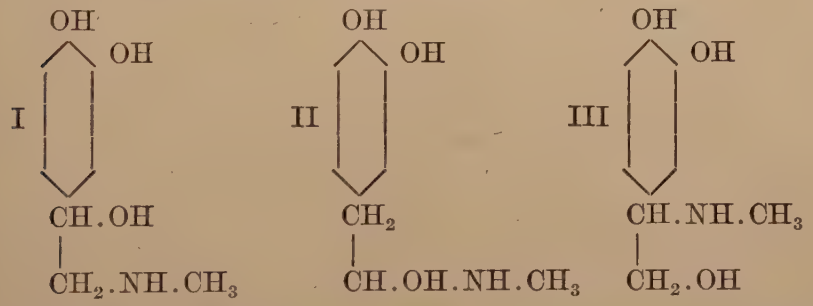
* Aldrich pointed out that, if one benzoyl group was removed from Abel's formula and the H was replaced, the resulting formula would be close to his. Abel(*e*)(*f*)(*i*)(*k*) admitted this, but took the position that what he called native epinephrin, or epinephrin hydrate, and which was adrenalin, should have the formula $C_{10}H_{13}NO_3.\frac{1}{2}H_2O$. Bertrand showed that Abel's analyses of his later product could just as well be explained by the formula $C_9H_{13}NO_3$ as by the formula $C_{10}H_{13}NO_3.\frac{1}{2}H_2O$. Other workers corroborated Bertrand's results and showed there was no water of crystallization (Pauly(*b*); Barger and Ewing(*a*) also Abderhalden and Bergell(*b*)).

Synthesis of Adrenalin

By fusing adrenalin with KOH, protocatechuic acid (Jowett) and pyrocatechol have been obtained (Takamine, von Fürth). On oxidation with $KMnO_4$, it yields methylamin, oxalic and formic acids (Jowett); treatment with concentrated acids or NaOH also yields methylamin (von Fürth). After methylation with dimethyl sulphate, oxidation with $KMnO_4$ produces veratric acid (3;4 dimethoxy benzoic acid) and trimethylamin, while the action of methyl iodid and alcoholic sodium on adrenalin, by means of bisulphite, produces vanillin, so that the complexes $C_6H_3(OH)_2.C$ and $NH.CH_3$ (methylimid) must be present in adrenalin. The latter group is in the side chain, not attached to the benzene nucleus, because it splits off so readily. As adrenalin yields tribenzoyl- and tribenzensulphon-derivatives it presumably contains 3 hydroxyl groups, one of which is in the side chain.

Friedmann showed that von Fürth's compound tribenzene-sulphonyl-adrenalin, which was optically active, lost its activity on oxidation to a keto-compound and argued that adrenalin possessed a secondary alcohol grouping. Pauly believed that the NH_2 group was of a secondary nature, because adrenalin in alcoholic solution reacts with phenyl mustard oil under conditions where the OH group seems indifferent so that the H was in direct relation to a carbon atom. He showed that adrenalin is optically active, hence contains an asymmetrical carbon atom in the side chain.

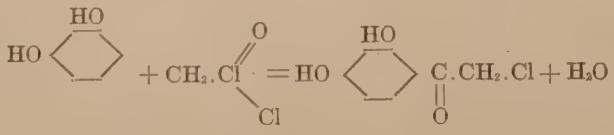
On these data, 5 possible groupings were proposed by Pauly and of these, three seemed the most acceptable.

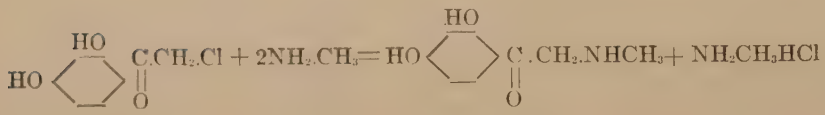


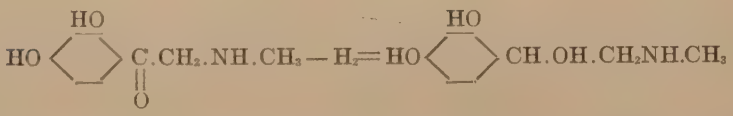
The first is more probable, because methylation and oxidation of the second compound would produce homoveratric acid ($C_6H_3.(OH)_2CH_2.CO_2H$) and the third arrangement would not so readily explain the formation of pyrrol and of skatol. A compound with the third arrangement has no pressor activity (Stolz).

The synthesis has been carried out, first by Stolz(*a*), later but independently by Dakin(*a*)(*b*). Stolz's synthesis is patented by Meister, Lucius and Brüning. This is the only method which is at present suitable for commercial work. The method is founded on the work of Dzierzgow-

ski, which showed that if pyrocatechol is heated with chloracetyl chlorid, chloracetylpyrocatechol is formed. When this compound is condensed with methylamin, and the resulting methylamin-acetyl-pyrocatechol is reduced with aluminum amalgam, or electrolytically, an amino alcohol is obtained which answers the demands of the first formula and which has many of the qualities of adrenalin, but is optically inactive.







One trouble with this synthesis is that the NH_2 group is easily split off (Stolz(*b*)).

Other synthetic methods have been proposed, i.e., methylating the base 3:4 di-hydroxy-phenylethanolamin or arterenol. The latter may be made by reducing amino-aceto-pyrocatechol or by reducing the cyanhydrin of protocatechuic aldehyd.

The methylene and dimethyl ethers of adrenalin have been synthesized, but these cannot yet be directly converted into adrenalin (Barger and Jowett; Barger; Barger and Ewins(*b*); Tutin, Taton and Hann; Mannich; Pauly(*c*); Pauly and Neukam; Böttcher).

Recently Nagai has patented a method for the manufacture of adrenalin by condensing protocatechuic aldehyd with nitromethane in the presence of weak inorganic or organic bases, which he does not specify, and then reducing the resulting di-acetyl-di-hydro-phenyl-nitro-ethanol with Zn dust and acetic acid, in the presence of formaldehyd. The di-acetyl adrenalin, when hydrolyzed by HCl, gives adrenalin hydrochlorid.

The study of the synthesis of adrenalin has attracted attention to two other synthetic compounds—homorenon or w-ethylamino 3:4 di-hydroxy-acetophenon $(OH)_2C_6H_3.CO.CH_2NHC_2H_5$ and epinin or 3:4 dihydroxy-phenylethyl methylamin $(OH)_2C_6H_3CH_2CH_2NH.CH_3$. Homorenon exerts a pressor action about like natural adrenalin, while epinin is about $\frac{1}{8}$ as active.

A number of other pyrocatechol derivatives exert a pressor action and several have been used commercially; thus methylamino-acetylcatechol

acts much like adrenalin although it is much less active (1-100). Dakin found that hydroxyethylmethylamin, which is the side chain in adrenalin, exerts slight, if any, pressor activity, while pyrocatechol is active to some extent.

A quinolin derivative β-amino-α-hydroxy (quinolyl 4) ethan, is claimed to exert an action on blood pressure like homorenon.

Synthetic adrenalin differed slightly from the l-adrenalin in that the melting point was lower and it formed a well crystallizable oxalate. Qualitative physiological tests showed it to exert all the physiological actions of the natural base. Some of the clinical reports at first indicated that synthetic adrenalin was even more active than the natural variety, but this was probably due to the greater purity of the preparation used and Biberfeld(*a*), who studied the action of synthetic adrenalin on rabbits, claimed it was as active as l-adrenalin, but Cushny(*b*)(*c*) repeated the experiments on blood pressure, using dogs, and showed that the synthetic variety was only one-half as active as the natural form and that rabbits were not suited for repeated injections such as had been used for this test, as they become tolerant to the action of adrenalin.

Schultz tested commercial samples of synthetic (dl)suprarenin and compared them with adrenalin, purified by Abel's method. He found their pharmacological action was in relation of 2 to 3. There might be some question whether the samples of synthetic suprarenin sent by the manufacturers to Cushny might not have been purer than those bought on the market by Schultz and this might explain the slight differences between the results of Cushny and of Schultz.

By means of tartaric acid, Flächer separated synthetic suprarenin into bitartrates of the d- and l- forms. The separation may also be carried out by means of *Penicillium glaucum*. The dextro-form can be racemized by treatment with acids and, by again separating, the yield of the levo-rotatory form may be increased.

Cushny tested d-adrenalin and found it 1-12 as active as the l-form both as to its action on blood pressure and in its toxicity. Under these conditions the manufacturers decided to market only the l-form under the name "synthetic suprarenin."

It might be of interest to see if the d-adrenalin has any of the properties which Abel ascribed to alkaloidal epinephrin. It gives the chemical reactions of the levo-variety (Borberg). So far as we know d-adrenalin has not been found in the suprarenal gland or its extracts. d-Adrenalin is much less toxic than the levo-rotatory variety and, in mice, its injection seems to render them more resistant than usual, to the latter. It was claimed to lessen or annul the pressor action of the natural variety (Abderhalden and Slavu; Abderhalden and Kautzsche; Abderhalden, Kautzsche and Müller; Ogawa, Waterman(*b*), Frohlich(*a*)).

Properties of Adrenalin

Natural adrenalin melts with decomposition at 211-212° C (uncorr.); the synthetic variety melts at 208°; the bitartrate of the synthetic base, melts at 149° C. Water at 20° C dissolves 0.0268 per cent.

It is almost insoluble in the usual organic solvents, but dissolves in warm ethyl oxalate and also in benzaldehyd (Abel(*e*); Barger and Ewnis). On long standing the base gives off volatile compounds (Abel(*f*)). According to Gunn and Harrison(*a*), adrenalin when treated with an excess of NaOH gives off an odor like that of PH_3. Warmed with chloral and caustic potash it produces an isonitrile odor. The salts are usually amorphous and deliquescent. A borate is claimed to be stable and not precipitable by NH_4OH (Imray(*b*)). Pauly has prepared a crystalline urate, but the most used crystalline salts are the bitartrate and the oxalate. A crystalline hydrochlorid may be obtained by dissolving the calculated amount of the synthetic base with the proper amount of alcoholic HCl and setting the solution aside with frequent agitation. This salt melts at 157° C (B. P. 1907).

Natural adrenalin is optically active and turns the plane of polarization to the left. Bertrand(*a*) — 53.40, Taveau, quoted by Schultz, 1909, — 51.40, Flächer, — 51.30, Abel and Macht.

Like pyrocatechol, adrenalin solutions show an ultra violet absorption spectrum (Dhéré).

Adrenalin reduces Fehling's solution. Its solutions readily oxidize, especially if minute quantities of ferric salts are present (Gunn and Harrison(*b*)). Oxidation is favored by the glass containers. It especially occurs in alkaline solution so that commercial solutions are usually made slightly acid, i. e., acid solutions of the hydrochlorid. A stable solution can also be made by the use of aldehyd or a keto-alkali bisulphite (Straub(*a*)). This coloration is associated with a loss in physiological activity (Liven, Schultz(*c*)). Apparently, the Roentgen rays do not change the activity of adrenalin solution (Ludin). Commercial adrenalin gives a reaction with diazobenzensulphonic acid (Pauly's Reagent). The closely related compounds, epinin, tyramin, etc., also give this reaction.

Aqueous solutions of adrenalin chlorid can be sterilized by heat (Rowe). Some commercial solutions contain sulphites (Puckner), but solutions of adrenalin chlorid were usually preserved with chloretone. Commercial solutions vary greatly in their activity (Sollman and Brown).

The ease with which oxidation occurs is partly due to the pyrocatechol nucleus and the color reactions used for its identification are usually due to oxidation. Like other pyrocatechol derivatives, adrenalin reacts with ferric chlorid in neutral or slightly acid solutions, by the production of a green color, which changes to violet and red (Weinland and

Binder(*a*)(*b*)). Acids and an excess of the iron solution interfere with the iron reaction (Boulud and Fayol, Meyer). In the presence of sulphanilic acid the iron reaction becomes more sensitive, but then produces a reddish brown to brown color instead of the green (Bayer(*a*)). Falta and Ivcovic showed that, on adding alkali, the green color in the iron chlorid test changes to a red and they believe this response is more sensitive than the simpler one.

Cameron gives the limit of sensitiveness of this reaction as 1 to 40,000, but the green color is hard to recognize in great dilution (Battelli). Borberg advises the use of dilute iron chlorid solution and claims it will respond to dilutions of 1–300,000, but the green color ceases at 1–100,000.

In the presence of air, solutions of adrenalin gradually oxidize and take on a pink color. This occurs rapidly in alkaline solution or in the presence of oxidizing agents, oxidases, etc. (Abderhalden and Guggenheim; Neuberg(*c*), Gessard).

In contact with iodin solutions, adrenalin solutions take on a rose or pink color, much as they do from long standing in the air, so that this color change is presumably due to oxidation (Lépinois). This test may be satisfactory for determining the amounts of the pressor compound, when pure, but is not satisfactory with aqueous extracts of suprarenal glands (Abelous, Soulié and Toujan(*a*), Seidell).

In the presence of certain salts, mercuric chlorid produces a rose red color. The salt here acts as a catalyst and forms free hydroxyl ions. The most suitable salt is probably sodium acetate (Ewins). This response to such mercuric chlorid solutions is known as Comessatti's reaction and is produced by dilutions of even 1 to 400,000 (Comessatti(*a*)(*b*)). When tested with Grimbert and Leclere's reaction, i. e., sodium acetate and $HgCl_2$, adrenalin gives a red color. This response occurs with 0.01 mgm.

In the test of Fraenkel and Allers a rose red color is produced in solutions of adrenalin by heating, below boiling, with an equal volume of n/1000 potassium bi-iodate and a few drops of dilute phosphoric acid. It occurs even in dilutions of 1–300,000. In strong solutions the color may take on a violet tint. Free iodin seems to play a part in this reaction.

A rose red color is also produced in dilute adrenalin solutions by warming with potassium persulphate when the concentration of the persulphate reaches about 0.1 per cent. This reaction occurs with extracts of the crude glands. It is sensitive in dilutions of 1 to 5,000,000 of the pure pressor compound and proteins do not interfere with it (Borberg). Erwins finds a distinct parallelism between the depth of this reaction and the pressor activity of suprarenal extracts (Pancrazio).

Other oxidizing agents, potassium ferricyanid, potassium permanganate (Gautier(*a*)), manganese dioxid (Zanfrognini), osmic acid (Mulon(*d*)), copper sulphate and potassium cyanid, sodium nitrite (Bor-

berg), gold chlorid (Gautier(*b*)), silver nitrate (Laignel-Lavastine(*a*)), have been used for determining the presence and, in some cases, the amount of adrenalin. According to Borberg(*a*), oxidizing reagents respond to dilutions of 1–300,000, but beyond this the response is doubtful.

Like other hydroxybenzenes, adrenalin gives a red color with a solution of uranium nitrate and ammonia (Toujan(*b*)).

Quantitative Determination of Adrenalin

Folin's reagent, which consists of a solution of 100 g. sodium tungstate in 750 c.c water with the addition of 80 c.c. of an 85 per cent phosphoric acid solution, gives a blue color-reaction with adrenalin solutions and responds to a dilution of 1 in 3,000,000 (Folin, Cannon and Denis).

A very convenient method for determining the amount of adrenalin in commercial solutions is by determining the amount of the pressor activity of an unknown solution and comparing this rise with that produced by a solution of a known strength (Houghton). Elliott(*d*) claims that by this test, on decerebrate cats, he can determine the amount of adrenalin present in solution to within 0.03 mgm., and perhaps within 0.01 mgm. The response of Folin's reagent is about that of the test made by Elliott's method.

Cameron has shown that the smallest amount of adrenalin which will cause a definite and invariable rise in blood pressure in rabbits weighing about 2,000 g. is 0.00062 mg. or 0.0003 per kilo. In cats, Ehrmann found that the intravenous injection of 0.1 mg. caused a rise which was just appreciable. Abel and Macht showed that in a dog (6 kgm.) 0.000008 g. caused a rise of 26 mm. Hg. The blood pressure method is not suited for determining the amount of adrenalin in serum (Borberg).

Strips of the cat's intestine are very sensitive to adrenalin. Magnus showed that longitudinal strips of cat intestine are inhibited by adrenalin even in dilutions 1 to 20,000,000 (Magnus). The intestinal method was used by Cannon and his co-workers for the detection of minute amounts in the blood. Later, Cannon used the denervated heart for this work. Intravenous injection of adrenalin, 0.001 mg. per kilo a minute, increased the heart rate 28 beats per minute.

Strips of rabbit intestine are as sensitive as those taken from the cat (Hoskins). The intestinal strip method is more specific for adrenalin than are the other biologic tests. At times, certain pituitary preparations relax intestinal strips (Bayer, and Peter).

The frog eye test of Meltzer and Ehrmann does not yield results, satisfactory for all cases of assay and frogs vary in their sensitiveness (Borberg). Schultz finds it a reliable method of assay, but less delicate

and more tedious than the blood pressure method. However, numerous other compounds dilate the pupils.

Hoskins finds that the direct application of adrenalin to the iris yields a sharper reaction than when it is applied to the corneal surface.

Strips of blood vessels sometimes respond with 1–100,000 adrenalin, but the maximal results are obtained with concentrations of 1 to 50,000. However, this method is not satisfactory for determining the amount of adrenalin in blood, because other vasoconstrictor substances, which are normally present in the blood, influence it (Schultz, Schlayer).

Stewart and Harvey believe that the Laewen-Trendelenburg reaction with frog blood vessels is the most sensitive test for adrenalin, when in pure solution, as it responds to dilution of 1 in 40,000,000.

The test on uterine strips may not always be satisfactory, at least, when testing for adrenalin in serum (Falta and Fleming; Stewart). The uterus is sensitive to mechanical stimulation and is at times erratic in its reactions. Its tendency to undergo spontaneous rhythmic contractions may interfere with its use (Hoskins). The reaction is not very specific, as extracts of various organs of the body give it.

Amount of Pressor Compound Present

Abel estimated that moist beef glands contain 0.3 per cent and as 1 part of the dried glands corresponds to 6 of the fresh ones the dried glands should, on this basis, contain 1.8 per cent (Abel). Hunt's experiments indicated that the dried glands contained about 1.5 per cent.

Using Folin's reagent and controlling this by the blood pressure test it has been estimated that sheep glands contain about 2.5 mg. per gram gland, calf 3.4 mg., cattle 3.9. Battelli, using the ferric chlorid colorimetric method, estimated calf suprarenals to contain 0.174 per cent. Rat suprarenals contain about 0.073 mg. per 100 gm. body weight (Herring). Rabbits contain 0.083 g. per kilogram, while guinea pigs contain 0.229 g. per 1000 kgm. body weight (Ornstein). The amount of the pressor compound varies throughout the year (Seidell and Fenger). In manufacture, using glands of cattle freed from fat, the actual yield is from 0.095 to 0.103 per cent, while sheep glands yield 0.08 per cent. Hog glands yield half the amount that beef glands will yield (Armour and Company).

According to Elliott, the adult human gland contains about 0.1 per cent of the pressor compound, i.e. 8–9 mg. in the two glands (Lucksch), while Ingier and Schmorl, using mainly Comessatti's method, or a modification of it, estimated 4.66 mg. in cases of death by accident. The glands in the adult weigh about 5 g. (Barger). Elliott finds at birth that the pressor compound is almost absent from the suprarenal medulla, but is present in the paraganglion aorticum; thus this organ which weighed 0.11 g. con-

tained 0.24 mg., while the suprarenal, which weighed 2.7 gm., contained 0.01 mg. This absence of epinephrin in human fetal glands has been confirmed (Lewis) although Svehla found it in the suprarenals of the fetal calf, and Fenger using colorimetric methods claims that the fetal calf contains as much as the adult. Barger suggests this may be explained by the presence of a physiologically inert precursor of adrenalin which gives its color reactions.

Synonyms of Adrenalin

As adrenalin became a commercial success various firms began to market its solution, necessarily under other names. This led to litigation which was finally decided in favor of Takamine (Amer. J. Pharm.). The final decision of the court rested on the product, not on the process (*Oil, Paint and Drug Reporter*). And in viewing this decision it is well to consider the early work of Holm.

Unquestionably the discoverer of a pure compound has a right to name his product, but it is shown by Abel's work that Takamine's adrenalin is not chemically pure and the results of the analysis which Takamine made did not coincide with those obtained from the pure active compound, so that on Takamine's basis alone there would be no necessary reason to retain the name. However, Aldrich, who first obtained the base pure and made the correct analysis, adopted this name, although Abel, previous to both, had obtained very active salts and whose formula, after the benzoyl group, had been removed, was closer to that of Aldrich than was the formula of Takamine, had used the name Epinephrin.

As the names for adrenalin, or its solutions, were multiplying rapidly and it was becoming a burden to remember these various names, hemisin, adnephrin, adrin, suprarenin, suprarenalin, caprenalin, paranephrin, etc., the Council of Pharmacy and Chemistry of the American Medical Association adopted the name Epinephrin for this base, partly to avoid further confusion, partly to give Professor Abel his just recognition, partly because this name had not been copyrighted, and partly because this was the first name used for the pressor substance in this country, while the term Adrenalin is a proprietary name (*J. Am. M. Ass.*, Braithwaite, Maben). The Council of Pharmacy and Chemistry of the American Medical Association adopted the name Epinephrin as a generic word.

Several large drug firms are spending much money in research work and there is some question as to how much right we have to change the names of compounds discovered by them and thus deprive them of some of their legitimate profits and whether such a change would not discourage commercial research, but in the case of epinephrin this does not seem to hold because of the work of Abel.

At first the English followed our change in name, but in spite of the

Anatomy, Embryology, Comparative Anatomy, and Histology of the Suprarenals

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NEW YORK

Anatomy

Gross Morphology and Relations.—Like most endocrin organs, the suprarenals are subject to great variation. They weigh together about eight or nine grams. In women they are rather smaller than in men. Of the two, the left is usually the larger; but the difference is referable chiefly to the cortex. On section the outer, cortical part can easily be distinguished by its yellowish color, which is due to its contained fat and lipoid. The medullary portion, by reason of its greater vascularity, is reddish brown. Each suprarenal fits like a cap on the mesial anterior pole of the kidney (Fig. 1). Their ventral relations with respect to the abdominal cavity differ. The left suprarenal gland is covered with peritoneum and is associated with the spleen, the stomach, and the tail of the pancreas. It is sometimes in contact with the splenic artery and vein. The right suprarenal is in relation with the liver, the inferior vena cava, and the duodenum. Both of them rest posteriorly upon the diaphragm and laterally upon the kidneys. They possess a slight but firm capsule, and are embedded in the renal adipose tissue. Each has a definite hilus on its anterior surface, through which the chief suprarenal vein leaves the gland.

Accessory Suprarenals.—Accessory suprarenal glands are of common occurrence. Strictly speaking, they contain both cortical and medullary substance, but they may consist of either alone. When they consist of medulla only, they should perhaps be classified with the other persistent sympathochromaphil tissue. They are quite small in size, seldom more than one centimeter in diameter. While they may occur in almost any part of the abdomen, they are usually found in the neighborhood of the

suprarenal glands and in association with organs, like the sex glands, which originate near them.

Their Formation.—During the course of the embryonic development of the suprarenals the ingrowth of medullary elements, as described in later paragraphs, frequently results in the splitting off of portions of the organ, resulting in the formation of accessory suprarenals, which usually remain in the neighborhood of the parent organ. Occasionally, however, they become associated with structures that change their position

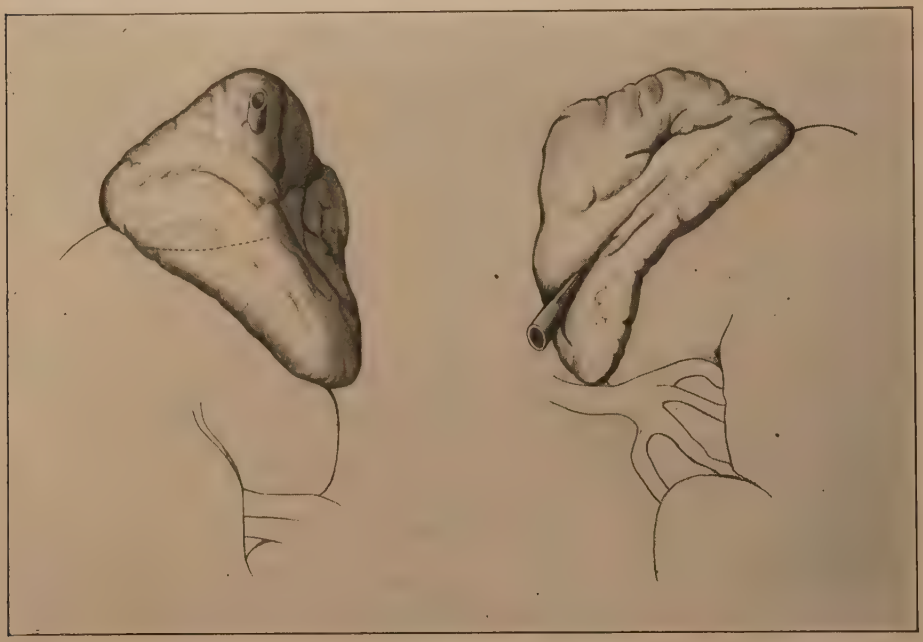

Fig. 1. Anterior surfaces of human suprarenal glands, after Cunningham.

in the course of development. In this way their association with the spermatic vessels and epididymis, and with the ligamentum latum of the female is explained.

Zuckerkandl(*b*) has shown that accessory suprarenals may also be produced by the separation of portions of the cortex, which, on this account, are often composed of the zona glomerulosa alone. They are found embedded in the substance of the principal organs, or scattered over their surface, and should not be confused with adenomata. The reasons for the separation are not so well understood. It is probably brought about by the migration of the cells, with an intervening deposit of connective tissue. Biedl thinks that they should be called "accessory interrenal bodies," since they consist for the most part of cortical or interrenal substances.

Meyer has recently discovered a well formed intracranial adrenal,

containing glomerular, fasicular, and reticular zones, as well as characteristic medullary tissue.

Blood Supply of the Suprarenals.—The adrenal is said to be relatively the most vascular organ in the body, receiving about six times its weight of blood per minute. The blood supply usually springs from three sources. The superior suprarenal artery arises from the inferior phrenic artery, the middle suprarenal from the aorta, and the inferior suprarenal from the renal artery. All three anastomose freely. The branching of the arteries within the glands is fully described by Flint. The capillaries are large and sinusoidal, that is to say, they are as large as venules, but possess only endothelial walls. They pass into veins, receiving tributaries from the capsule, cortex and medulla, which run together forming the central vein of the gland which emerges at the hilus. Each suprarenal is also surrounded by a rich venous plexus which communicates with a similar network about the kidney. On the left, the plexus discharges into the renal vein, and on the right, into the inferior vena cava.

Lymphatics.—The lymphatics are also abundant. Their close association with the secreting cells has been studied by Kumita. They form a rich network in the medulla, which communicates, through the cortex, with a subcapsular network. Lymph is discharged into the lymph glands along the aorta. There is also a variable but important connection, on the left side, with the posterior mediastinal glands.

Innervation.—The nerve supply of the glands is but little understood. It is known, however, that they receive their chief innervation directly from the splanchnics (Fig. 2). Fibers from the suprarenal plexus enter them. Assertions to the effect that they receive twigs from the vagi and phrenics are probably erroneous. The splanchnics carry myelinated preganglionic fibers, arising from cells in the lateral column of the spinal cord, as well as postganglionic fibers from cells in the thoracic ganglia. According to Falta(*d*), the right suprarenal in rabbits is supplied by the right and left splanchnics, while the left is innervated by the right splanchnic only. It is not known whether there is any difference between the two in man. The fibers from the suprarenal plexus are probably all postganglionic and unmyelinated. Coming from these sources, they form a network in the connective tissue surrounding the organ and then penetrate into it, running in the connective tissue septa between the cell columns in the cortex. Their subsequent behavior has not been worked out in detail. Groups of sympathetic cells occur normally in the medulla, and occasionally in the cortex, with which they come into relation. We have reason to believe that fibers terminate about the blood vessels and in contact with the secreting cells in both the cortex and the medulla. According to Burton-Opitz and Edwards, the evidence advanced in favor of the existence of vasodilator fibers is not sufficiently convincing.

The return pathway is quite unknown, but we would expect to find visceral sensory fibers of the spinal ganglion cells running into the cord through the dorsal roots. Elliott(*d*) believes there is a center controlling

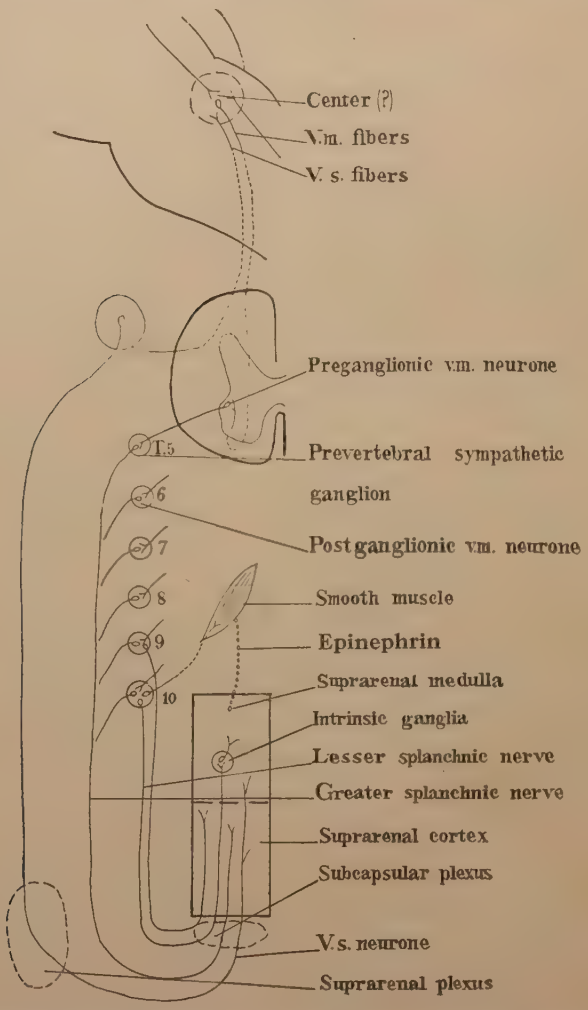

Fig. 2. Scheme of the probable innervation of the suprarenal gland; *v. m.*, visceral motor and *v. s.*, visceral sensory.

the secretion or discharge of epinephrin somewhere near the bulbar vasomotor centers. Others place the center in the subthalamic region. Wherever it may be, it probably receives cortical impulses from above and excitations from the body generally, and discharges into the suprarenal as indicated (Fig. 2). The stimulation of an afferent nerve, like the great sciatic, is said to bring about secretion of epinephrin (questioned by Stewart and Rogoff(*j*)), as is also the stimulation of the splanchnics themselves

(Dreyer, confirmed by Stewart, Rogoff, and Gibson; denied by Gley and Quinquaud(*b*)).

Independence of the Cortex and the Medulla.—That the two parts of the gland are independent structures is indicated by a variety of observations and believed by most endocrinologists. As described in succeeding paragraphs, they are distinct in embryonic origin. Moreover, we may get aplasia of the cortex while the chromaphil tissue remains intact, as in the case described by Apert, and conversely, the medullary substance was found to be completely wanting in the five cases of congenital hydrocephalus described by Czerney. The cortical and the medullary substances, therefore, vary independently.

Relation of Cortex to Lipoid Formation.—There is some reason to believe that the growth of the cortex is related to that of the brain, and especially to the development of its lipoid substance. "The suggestion that the suprarenal cortex may be a seat of manufacture of the lipoids of the body, and may especially be related to the formation and development of the myelin of the medullated nerve fibers, is attractive. And the fact that in the human fetus and infant so large a development of the suprarenal cortex occurs—which is missed in the anencephalous monster—seems to indicate a connection between the development of the substances formed in the cortex and those constituting the cerebral hemispheres. But against this idea, we have the observation of Elliott and Armour that the superadded part of the suprarenal cortex in the fetus does not contain the doubly refracting lipoid substances which are characteristic of the ordinary cortical cells. Nor does the doubly refracting lipoid matter occur in all animals; in many species it is absent. This is the case with all adult ruminants examined, although it occurs in some in the young state." (Quotation from Schafer(*b*).)

Embryology

The suprarenal glands, like the hypophysis, are developed from two distinct sources.

Origin of the Cortex.—Soulie finds that the cortex first makes its appearance in the embryo of six millimeters, i. .e, at the fourth week of development. The cortical cells appear as a series of buds, which arise from the celomic epithelium in the dorsal body wall. These buds grow inward into the mesoderm and lie ventral to the aorta. At eight millimeters the glands are definitely separated from the parent tissue, and at nine millimeters have acquired their own blood supply. Later, the buds fuse and form a ridge of tissue projecting from the wall at the root of the mesentery on each side just mesial to the mesonephros. The suprarenal ridge thus formed extends as far forward as the dorsal pillars of

the diaphragm, reaching almost the full length of the body cavity. Later, by a process of degeneration of some of the tissue and arrest of development, while the remainder of the body continues to develop, the glands come to have the relatively small size of their adult state.

Origin of the Medulla.—The cells making up the medulla are derived from the primitive nerve tissue. At an early stage of development a mass is separated from the lateral wall of the neural plate to form the neural crest. From this mass cells migrate to the neighborhood of the aorta. By the time the embryo has reached a length of seven millimeters the migration is well under way. At nine millimeters the ganglionated cord and the sympathetic nerve plexuses of the adult can be recognized. At sixteen millimeters the outlying visceral ganglia have been established. In close association with these structures are the cells which give rise to the chromaphil tissues. Indeed, in the earlier stages, the two sorts of cells are indistinguishable. They form together the sympathochromaphil tissue. Later, as the two types become recognizable, they form the sympathoblasts and the chromaffinoblasts. The chromaphil bodies develop early, before the sympathetic cells proper, or the medulla of the adrenals can be differentiated. When the embryo has reached a length of nineteen millimeters the chromaphil cells have begun to penetrate well into the cortical mass described in the preceding paragraph. At nine and a half centimeters the chromaphil cells appear as islands scattered through the cortical tissue, but some of the cells have already reached the central vein and formed the nucleus of the medulla. From this stage on, development consists of further penetration of the chromaphil cells to join the central mass. The process is not entirely completed at the time of birth.

Appearance of the Chromaphil Reaction.—It is not until between the third and the fourth month that the medullary substance acquires its chromaphil reaction and may therefore be considered functional. That such reaction is evidence of secretory potential, is shown by the observation that in the fully formed gland the coloration disappears as the epinephrin is exhausted. Moreover, Lewis has been able to detect epinephrin in extracts of the suprarenals of full term fetuses.

Differentiation of Cortex.—The differentiation of the cortex takes place very slowly. According to Zuckerkandl, "the zona reticularis may be recognized in an embryo of fourteen and a half millimeters." Elliott and Armour consider the enormous relative size of the suprarenals in fetuses to be due to the high development of a portion of the cortex adjacent to the medulla, which they call the boundary zone. The cells in the boundary zone are devoid of lipoid at this stage of development. The lipoid is restricted to a very thin layer of cells near the surface of the cortex. Later on, the cells of the boundary zone accumulate fat and become typical zona glomerulosa between the second and third years.

The Paraganglia.—It is interesting to note that sympathochromaffin tissue also develops into other organs in addition to the suprarenal glands. It gives rise to the so-called chromaphil bodies, which are also referred to as paraganglia, owing to their topographical relationship to the sympathetic ganglia. They are thought to vary in number from five to twenty-five or even thirty. The largest are the aortic bodies, about one centimeter long, situated in the vicinity of the abdominal aorta between the kidneys (Fig. 3). All of them, with the possible exception of the carotid body, attain their maximum development before birth and later undergo retrogressive changes. In adults they can rarely be detected without microscopic examination. Biedl and Wiesel have shown that extracts of these bodies have the same physiological action as extracts made from the medulla of the gland, which observation is confirmed by the more recent work of Fulk and Macleod.

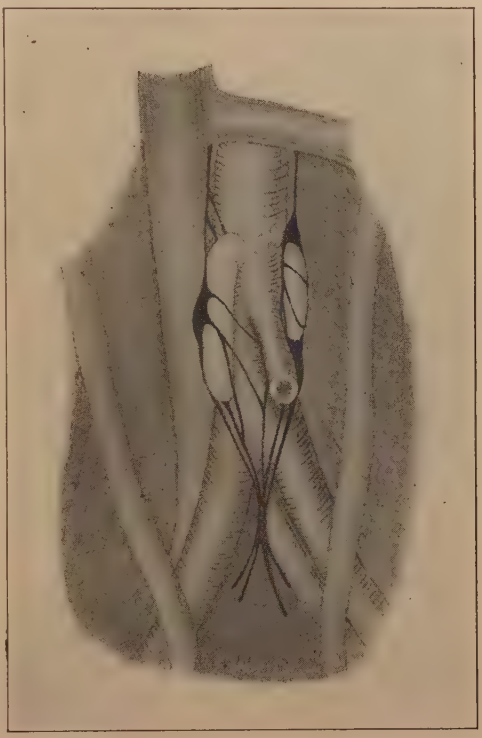

Fig. 3. Aortic bodies of newborn baby from Piersol, after Zuckerkandl.

Variations in the Suprarenals under Different Conditions.—*With Sex Anomalies.*—Excessive development or hyperplasia of the cortex of the suprarenal glands has been found by Glynn and others to be associated with the development of secondary male characters, such as hairiness, in females. This relationship is discussed at length in the section on clinical suprarenal syndromes.

Seasonal Variations.—Observations on seasonal variations in the weight of the suprarenal glands are on record. Stilling, for instance, found an increase in size in male rabbits during the breeding season; and, according to Glynn, Aichel has confirmed Nagel's observation of similar changes in amphibians and birds. Glynn is of the opinion that much the same alterations take place in human beings, but statistics are entirely wanting.

Sex Differences.—Hatai and Jackson are agreed that in the white rat there is a distinct sexual difference in the suprarenals(*b*), that they are relatively much larger in the female, especially during pregnancy and lac-

tation (Verdozzi). It is not apparent until about forty to fifty days of age (Donaldson). In man, however, it is generally thought (without much evidence) that they are larger in the male.

Variations form Endocrin Factors.—In rats the suprarenals undergo hypertrophy, especially in males, as a result of thyroid feeding (Herring, Hoskins(*b*)). Carlson has reported, however, that thyroidectomy also causes suprarenal enlargement. Castration causes an increase in the size of the suprarenals in male rats and a decrease in females (Hatai).

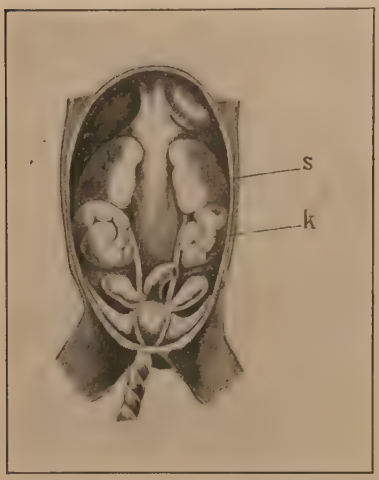

Fig. 4. Dissection of a three months' human fetus showing the relative size of the suprarenal (s) and the kidney (k), after Piersol.

Growth.—The growth of the suprarenals is very precocious (Fig. 4), and Jackson(*b*) has found that it is quite different in character from that of the thyroid and thymus glands. Instead of being gradual and progressive, it is extremely rapid during the third month, when the organs reach their greatest relative size; from then on they decrease, until in the adult they are reduced to about one one-hundredth of one per cent of body weight. The vigor of their growth energy is shown by the fact that they go on developing and even increase slightly in weight in young white rats held at maintenance level of body weight by underfeeding (Jackson(*a*)). A differential study of the cortical and medullary portions has very recently been made by Jackson.

Comparative Anatomy

Duality of Suprarenals.—Our conception of the dual nature of the suprarenal glands is sustained by our knowledge of their comparative anatomy. Phylogenetically the cortex and the medulla are entirely distinct organ systems and only become topographically associated in the higher forms. The changes are represented in the accompanying diagram.

Conditions in Various Phyla.—*In Invertebrates.*—In invertebrates the medullary portion is represented, perhaps, by certain large cells occurring in connection with the abdominal ganglia, which give the chromaphil reaction, and from which epinephrin may be extracted (Biedl, Gaskell(*c*)). Representatives of the cortical substances are, however, unknown.

In Fishes.—Both systems are found in fishes and are quite distinct

anatomically. In selachians the medullary part is represented by small paired masses of chromaphil tissue in close association with the sympathetic ganglia (Fig. 5). These have been commonly called "suprarenals," but it seems better to restrict the use of the term "suprarenal" to the two associated systems as they occur in the higher forms. The word "adrenal" has also been applied to them, and Biedl considers this to be not so objectionable, since, ignoring the old topographical meaning, it may be taken to signify that on extraction they yield "adrenalin." The cortex, on the

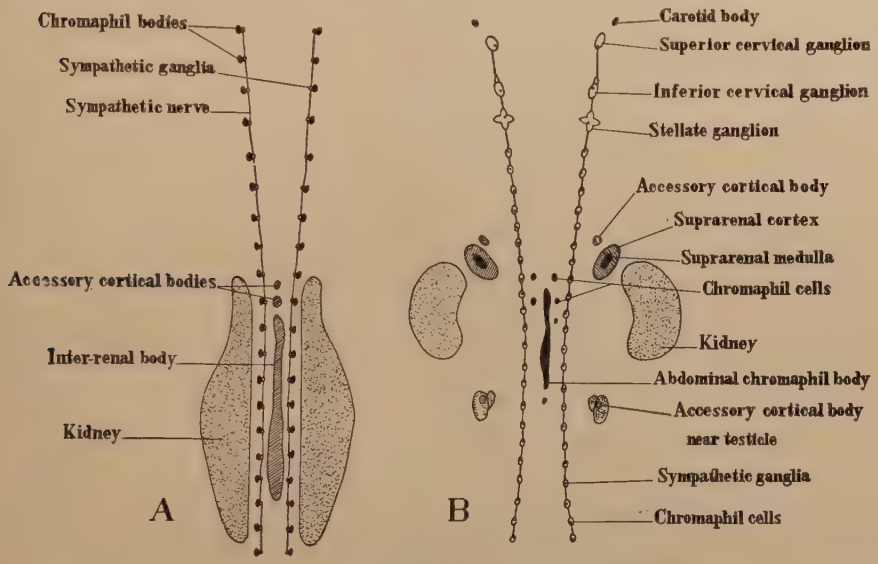

Fig. 5. Diagrams of the condition of the suprarenal apparatus in a selachian (A), and in man (B), after Vincent.

other hand, is represented by a much larger single median structure called an "interrenal body."

In Amphibia.—As we pass upward in the scale, these primitive relations are lost. A transitional condition is met with in amphibians, in which the close association of the adrenal (chromaphil) tissue with the sympathetic ganglia is to some extent lost and a partial connection with the interrenal system is effected.

In Reptiles and Birds.—In reptiles and in birds the association is still closer, but it is only in mammals that the adrenal tissue penetrates into the interrenal and becomes definitely enclosed by it, forming the medulla of the definitive suprarenal gland.

Even in man, all the adrenal tissue is not disposed of in this way, for some of it retains its independent condition, being distributed in various parts of the body, where it has already been discussed under the heading of chromaphil bodies. The genetic relationship, if any, between this

adrenal tissue and the epinephrin secreting poison glands of the toad, which also exhibit the chromaphil reaction (Shipley), has not been ascertained.

Quantitative Relations.—The relative amounts of the two tissues have not been accurately studied in phylogeny. Elliott and Tuckett point out "that the lower the animal in the vertebrate, or at any rate, in the mammalian series, the greater is the relative development of the cortex."

Constancy of Cell Types.—The different cell types are remarkably constant throughout the vertebrate scale, Rana esculenta alone containing a type of cell which is strongly acidophilic and which seems to be without counterpart in other forms.

Histology

The Cortex.—*Zones of the Cortex.*—In the cortex the cells are arranged in three groups called, from without inwards, the zona glomerulosa, the zona fasciculata, and the zona reticularis. These layers are subject to considerable variation in different animals, being much more distinct in some than in others. Mulon believes that in the guinea pig the glomerular zone is germinative and that the cells in it continue to multiply throughout life. This idea is supported by the studies of Graham, who believes that the zona glomerulosa and the outer cells of the zona fasciculata are the growth centers for regeneration in the adult. Unfortunately we have no reliable data for man on which to base an opinion. There are no trustworthy indications of a division of labor in the zones of the cortex with respect to either growth or secretion (Fig. 6).

Cell Types.—(1) *Clear Cells—Their Inclusions:*—(*a*) *Lipoid Substances.*—Two types of epithelial cells are often described in the cortex, the clear cells and the dark cells, depending upon their appearance in fixed and stained preparations. The clear cells in the guinea pig are the most numerous. They contain an abundance of rather large, fatty, spherical droplets which are highly refractile, stain with Sudan III, sometimes blacken with osmic acid, and are very soluble in essential oils. Their exact chemical nature remains undetermined. There is no reason to believe that they are the same in different species. They are often present in variable amounts in the different zones. According to Elliott and Tuckett, they are absent in sheep. These granules are dissolved out in ordinary preparations, thus giving a vacuolated appearance to the cells (illustrated in Fig. 7). Doubly refractile lipoid granules are also present, which produce myeline forms when liberated from the cells. Thyroid feeding is thought to bring about a reduction in the amount of lipoid. Ascoli and Legnani claim that the lipoid is increased by hypophysectomy (citation from Schäfer).

(*b*) *Pigment and Mitochondria.*—Pigment is of common occurrence, particularly in the zona reticularis. Mulon(*c*) has found that there are typical mitochondria between the granules of pigment and lipoid.

(*c*) *Reticular Apparatus.*—Pensa has discovered a dense, well defined cytoplasmic network, which he believes to be similar to the reticular apparatus described by Golgi and his students in many other cells. Holmgren has also described a network of clear canals, called trophospongium, within the cells, which is believed by some to be similar to the reticular apparatus of Golgi. Thus far, however, no experimental results have been recorded making use of the Golgi apparatus as an indicator of cell activity and cell injury. No trace of the apparatus can be seen in living cells teased out in salt solution.

Fig. 6. Section of a human suprarenal gland showing the capsule, glomerular, fasicular and reticular zones and medulla (magnification 110).

(*2*) *Dark Cells.*—The dark cells stain intensely with iron hematoxylin and have for this reason been called "siderophil." They also contain granules stainable with Sudan III. Mulon(*e*) thinks that the mitochondria have all gone into solution, which explains the uniform coloration of the cells with mitochondrial dyes. It is difficult to say whether Pensa observed the reticular apparatus in these cells or not.

(*3*) *Relation Between Light and Dark Cells.*—The relationship of these two cell types (light and dark) is under active discussion. All stages in transition between them may be distinguished. Both of them possess attraction spheres. It is uncertain whether they represent different phases of functional activity

or different stages of cytomorphosis. Our information concerning the conditions in man is especially unsatisfactory.

Secretory Antecedents.—Many consider the doubly refractile lipoid granules to be true secretion antecedents, but evidence is illusive. Da Costa is of the opinion that the mitochondria are changed into lipoid, which is somewhat similar to Mulon's view, according to which the mitochondria themselves are the secretion antecedents of a lipoid substance which completely impregnates the cells (dark cells) and passes through the intercellular spaces into the blood vessels. He thinks that the interstitial cells of the testis and ovary likewise produce a lipoid secretion. This interpretation is supported by the presence of an abundance of lipoid in all three, and by the fact that they are all developed from the nearby cells of the Wolffian ridge. The interstitial cells of the ovary are, however, said to be more easily destroyed by X-rays than those of the testis. The suprarenal cortex contains cholin, but it is unlikely that this constitutes a specific secretion.

Fig. 7. Cortex of human suprarenal gland showing the very intimate relation of the cells to the blood vessels and the vacuolated condition of the cytoplasm caused by the solution of the lipoid droplets (magnification 720).

The Medulla.—*Cytology.*—The epithelial cells of the medulla (Fig. 8) are arranged in a very irregular fashion in columns and clusters, surrounded with loose connective tissue, blood vessels, nerves, and lymphatics. They are in very intimate association with the venous sinusoids. The cells do not differ very much *inter se*. Definite types are not distinguishable as in the cortex. There are no structural indications of a division of labor in the different regions of the medulla. The internal architecture of the cells has been very carefully investigated in mammals. They contain numerous mitochondria and, occasionally, pigment and fat also. The nuclei are spherical and often somewhat larger than those of the cortical cells. A careful study of the reticular apparatus is much needed.

The cells possess definite attraction spheres toward one pole of the nucleus.

Microchemical Reactions.—According to the studies of Vincent(*d*), the chromaphil bodies, at least in the dog, are structurally fairly similar to the medulla. The cells are arranged in irregular columns and resemble those found in the medulla of the suprarenal. The cell columns are separated by connective tissue, blood vessels, and nerves. He records the presence of "homogeneously stained material which appears to resemble the colloid of the thyroid" in the form of droplets within the cells and in the intercellular spaces, but he gives no detailed information regarding it.

The cells of the medulla are characterized by four microchemical reactions.

Fig. 8. Medulla of human suprarenal gland illustrating the structure of the cells (magnification 720).

(*a*) *Chromaphil Reaction.*—The chromaphil reaction consists of a dark brown coloration when the cells are treated with chromium. This reaction is not given by any other cells of the body with the exception of the chromaphil tissues already mentioned and the poison glands of certain lower forms. It indicates the presence of epinephrin or some nearly related substance. Its chemistry is discussed by Ogata and Ogata. There has been a good deal of discussion concerning the element in the tissue which gives the reaction. Many consider it to be localized in certain minute granulations within the cells; others, however, regard it as a property of the ground substance in which the granules are embedded. In all probability both views are, in a measure, correct.

(*b*) *Ferric Chlorid Reaction.*—The perchlorid of iron reaction is also given by the medullary cells. When moistened with a drop of perchlorid they turn a beautiful green color. It is thought that the granulations within the cells possess an affinity for the iron, just as they do for the chromium. Since, as Da Costa remarks, the chromaffinity disappears more rapidly on putrefaction than the sideraffinity, it is quite

possible that we may be dealing with two substances, epinephrin itself and some forerunner.

(*c*) *Silver Nitrate Reaction.*—Macallum has extended Laignel Lavastine's observation that certain granules in the medullary cells reduce silver nitrate, and has claimed that the reduction is probably due to the presence of an antecedent of epinephrin, which he believes to be tyrosin. It is very interesting to note that Macallum has found that a similar reaction is given only by nerve cells, indicating that they too may possess the potentiality of epinephrin production, though in a much less marked degree.

(*d*) *Osmic Acid Reaction.*—Cramer describes a simple method for the demonstration of epinephrin within the cells through blackening with osmic acid. The granules thus revealed may be distinguished from the lipoid droplets by the solution of the latter in turpentine. He claims that these "adrenalin granules" pass into the blood vessels in glands stimulated by the injection of tetrahydronaphthylamin, and that they decrease with exhaustion of secretion. He asserts also that "in the various conditions demanding an increased functional activity of the suprarenals fine black granules, similar to the adrenalin granules of the medulla, and not dissolved by turpentine, appear in the cortex, especially in the layers of cells nearest the medulla. Whether these granules are actually adrenalin, or whether they are perhaps to be looked upon as precursors of adrenalin, is at present not possible to say. This fact is, however, clear evidence that the cortex participates in the functional activity of the medulla and that these two parts of the gland are not physiologically independent organs."

Secretory Changes.—Secretory changes have been repeatedly described. It has been found that following prolonged narcosis in man with the accompanying discharge of epinephrin, the chromaffin reaction is reduced. Falta(*d*) credits R. Kahn with the discovery that, after Claude Bernard's "piqûre" of the medulla oblongata, "the tingibility of the suprarenals to chrome salts in great part disappears and the contents of adrenalin markedly diminish." It is also known that, in the compensatory hypertrophy resultant upon the removal of one suprarenal gland, the chromaphil reaction is also more intense. Cevidalli and Leoncini state that the chromaphil reaction is less intense in the case of persons who have died slowly, with exhaustion of the adrenalin content of the gland. Their results, however, require confirmation.

Discharge of Secretions.—Many investigators have described the presence of material exhibiting the chromaphil reaction within the sinusoids and veins of the medulla, which they consider to represent the adrenalin secretion. Others, however, regard it as a simple coagulation of the blood plasma. Its total absence in the cortex, and its restriction in the medulla to the veins, are advanced as evidence in favor of its secretory

nature. The blood in the suprarenal veins contains epinephrin and exhibits a green coloration with sesquichlorid of iron (Vulpian's reaction).

THE CAROTID AND COCCYGEAL BODIES

Strictly speaking, the carotid body is merely an outlying portion of the suprarenal system proper, and might well be treated in connection with the accessory suprarenals and paraganglia. The coccygeal body, on the other hand, has apparently no relation to the suprarenals. Since Luschka's first description of them they have been conventionally treated together, however, and, as a matter of convenience, the two structures may be discussed in this place.

The Carotid Bodies

Anatomy

Gross Morphology and Relations.—The carotid bodies are small oval structures of a reddish color, about six millimeters long and two millimeters thick, situated near the bifurcation of the common carotid arteries. They are subject to considerable variation, and may be absent or so small as to escape detection. Frequently a gland is divided into two unequal parts, which are confluent below. It may be broken up into four or five parts. Each gland possesses a capsule bound down by connective tissue to the wall of the artery, which is slightly thickened at the point of contact. The body has a very rich vascular and nerve supply, the latter chiefly sympathetic, though it has been claimed, probably erroneously, that the glossopharyngeal, superior laryngeal, and hypoglossal nerves contribute fibers to it. Ganglion cells are found in the bundle of nerve fibers.

Embryology and Phylogeny.—Both ontogenetically and phylogenetically the carotid bodies are clearly composed of chromaphil tissue. Their development in man has not been carefully worked out. It has been found, however, that they are formed from sympathochromaffin tissue, which accumulates on each side of the body in the vicinity of the internal carotid artery, near the ganglion nodosum of the vagus. They have been found in most mammals which have been investigated. We regard them as vestiges in man of the chromaffin tissue which is relatively more highly developed in lower forms and, as such, they are comparable to the paraganglion aorticum. Luschka(*b*), who first recognized the gland as an entity, interpreted it as a "nerve gland," auxiliary to the sympathetic system. Shortly afterward, Arnold, as a result of further study, came to the conclusion that it is merely a network of blood vessels, the walls of which are composed of extra layers of epithelium. Stieda believed that the

carotid body developed from the epithelium of the branchial cleft and regarded it, therefore, as a gland. His recognition that the epithelium seemed to disappear in the later stages of development, however, later led him to doubt this conclusion. It has since been abundantly shown that the organ is not of epithelial origin.

Histology.—The characteristic cells of the carotid body are arranged in spheroidal clumps, imbedded in connective tissue. Kohn(*a*) has placed them in four groups, depending upon the density of the parenchyma:—

Cell Types.—*Compact Type.*—This consists of a single mass resembling a ganglion. It is with difficulty penetrated by a needle and is found in the cat.

Intermediate Type.—This group is not so compact as the preceding, nor so diffuse as the following. It is found, for example, in the ape.

Granular Type.—This is composed of scattered cell groups, as in man.

Diffuse Type.—This is sufficiently described by the name. It is found in the rabbit.

Schaper showed that the characteristic cells of the organ are neither gland cells, as earlier claimed, nor endothelium from the vessel walls. He disputed the claim that they are merely rudimentary structures, and suggested that they have some definite function.

Chromaphil Reaction.—By the application of chromium salts Stilling(*b*) showed that, as a matter of fact, the cells are of the same chromaphil type as those found in the paraganglia and the suprarenal medulla. He therefore designated the body a vascular gland analogous to the suprarenals. That the tissue in question is similar to that of the medulla was further shown by Mulon(*c*), in that extracts of the carotid body give a pressor vasomotor reaction, similar to that of epinephrin.

The Coccygeal Bodies

The coccygeal bodies are small masses of tissue, the largest of which rarely exceeds three millimeters in diameter. They are usually of spherical or lobulated shape, of a reddish color, and are situated immediately ventral to the end of the coccyx. The middle sacral artery is the best clew to their location (Fig. 9). They are highly vascular and are richly supplied with sympathetic fibers.

When the coccygeal bodies were first discovered by Luschka(*a*), he regarded them as ductless glands which had developed in part from the sympathetic nervous system. Störk has shown that this conception is quite erroneous, and that neither in fetal nor post-fetal life do the bodies give the characteristic chromium reaction. Schumacher has afforded conclusive evidence that the coccygeal bodies correspond to the glomeruli caudales of lower forms, which are developed as arteriovenous anastomoses.

This conclusion, with but slight modification, has been recently confirmed by Vallois and Perron. The origin in man is a local thickening of the branches of the medial sacral artery. The muscle fibers in the vessel walls have an epithelium-like appearance, and it is this peculiarity which led

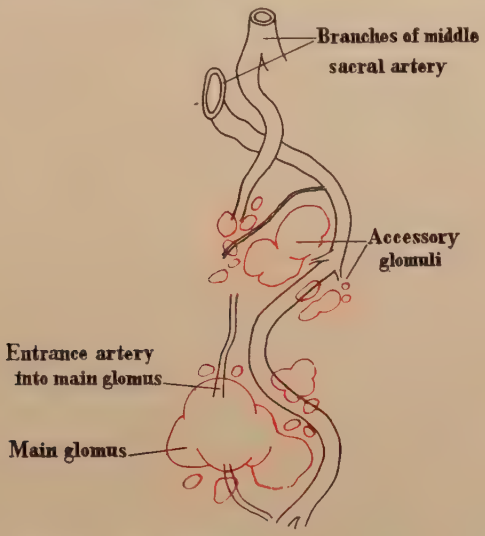

Fig. 9. Diagram showing the relation of the principal and accessory coccygeal bodies to the middle sacral artery, after Cunningham.

to the earlier conception of the structure as a gland. In reality, there is no reason for regarding the coccygeal body as in any way related to the endocrin organs.

Chemistry of the Suprarenal Glands . . *Albert C. Crawford*

Historical—Earlier Work—Later Work—Synthesis of Adrenalin—Properties of Adrenalin—Quantitative Determination of Adrenalin—Amount of Pressor Compound Present—Synonyms of Adrenalin—Distribution of Epinephrin—Chemistry of Chromaffin Tissue—Chemistry of Suprarenal Cortex.

statement of the English chemist, Jowett, that epinephrin and adrenalin were names for the same compound, they later adopted the name adrenin, presumably because Abel had used the term epinephrin for his inactive base as well as for the base of his active salts. The Germans have adhered to the trade name suprarenin, no doubt owing to the strong influence of the German commercial firms and their different attitude toward proprietary names.

Distribution of Epinephrin

Epinephrin has attracted much attention. Above certain concentrations it has been found to exert a marked pressor activity, but there is some question where normally such concentrations occur in the body and whether this compound under ordinary conditions is used by nature for functional purposes and whether it is not merely a stepping stone in the synthesis or degradation of other compounds. At present, we have no right to speak of epinephrin as the active principle of the suprarenal glands, but should call it an active principle, because in the suprarenal glands it occurs only in the medulla and the medulla may be destroyed without causing death, while destruction of the cortex is fatal and we have no proof that epinephrin is directly or indirectly formed by the cortex (Stewart and Rogoff; Wheeler and Vincent).

As pyrocatechol and its derivatives easily oxidize into dark colored bodies and as epinephrin also yields such products it has been suggested that the latter is the source of the black pigment in certain melanotic tumors, but epinephrin itself has not been found in such tumors (Neuberg, Jaeger, Bittorf, Adler). However, extracts of some contain a substance, designated a ferment, which decomposes epinephrin into a black pigment (Meirowsky).

Para-hydroxy-phenyl-ethyl-amin, a decarboxylation product of the amino-acid tyrosin, has a chemical structure somewhat like epinephrin and exerts a physiological action much like it. This action Barger and Dale name sympathomimetic (Dale and Dixon). It was suggested that the amino-acid tyrosin was the mother substance of epinephrin (Halles, Gessard). However, Ewins and Laidlaw show there is no real evidence for the view that it is formed in the body from tyrosin or other closely related bases. An amino acid, 3:4-dihydroxy-phenyl-alanin ($(OH)_2C_6H_3CH_2$-$CH.NH_2.COOH$), which has a structure related to epinephrin, has been found in *Vicia faba,* but this, like other amino-acids, is pharmacologically indifferent (Guggenheim, Funk).

It has been suggested, not proved, that epinephrin might be derived from the amino-acid tryptophan (Abelous, Soulie and Toujan), while Friedmann thought it might be derived from di-hydroxy-phenyl-methyl-serin or di-hydroxy-phenyl-serin (Rosenmund and Dornsaft; Knoop).

Popielski suggested that epinephrin existed in some labile combination with protein, while others thought that epinephrin might be derived from decomposition products of the lipins of the cortex (Boruttau), but as yet a mother substance for epinephrin has not been discovered. We have no reports of a thorough study of the suprarenal glands for amino-acids or their decarboxylation products. Leucin and tyrosin have been shown to be present (Lohman).

Chemistry of Chromaffin Tissue

The medulla of the suprarenal glands stains yellow, or brown, with chromic acid, hence is spoken of as chromaffin tissue. Tissues giving this reaction are found in the carotid bodies and elsewhere associated with the sympathetic nervous system (Gaskell, Stilling). However, unlike epinephrin, extracts of sympathetic ganglia cause a fall in blood pressure (Cleghorn).

It is believed that epinephrin, or a derivative of it, is the cause of this reaction, as a solution of potassium bichromate colors epinephrin crystals a brown color and this has been shown to be due to the formation of CrO_2 (Borberg; Ogata and Ogata; Stoeltzner). The intensity of the chromium reaction corresponds to the amount of epinephrin present (Elliott and Tucket; Ciaccio; Schur and Wiesel). Vincent believes that chromaffin tissue always yields epinephrin, or a substance with similar pharmacological action. The work of Ogata and Ogata indicates that the chromophil reaction is really a reduction due to epinephrin and they would substitute the name adrenalin tissue for chromaffin tissue.

Chromaffin tissue, in other localities than in the suprarenal glands, has been tested for the presence of epinephrin. Mulon claimed that he obtained a pressor effect from an extract of the carotid body of a horse. But Frugoni's injections in rabbits produced only a fall. However, Vincent believes it would be impossible to obtain a pressor response from carotid gland extracts as these glands contain so many tissues which would produce a fall, which fall would mask any possible rise.

Using the test on uterine and on intestinal muscles as their guide, Fulk and Macleod claim that extracts of the retroperitoneal chromaffin tissue reacts like epinephrin and such extracts raise the blood pressure (Biedl and Wiesel). Wells suggests that the production of epinephrin outside of the suprarenal glands may explain the discrepancies between the anatomic changes in the suprarenals and the clinical manifestations of a deficiency of epinephrin.

Abel and Macht have isolated large amounts of epinephrin (about 5 per cent) from the secretion of the parotid gland of the tropical toad, *Bufo agua* (Abel and Macht). However, "at no time in their life history do the epithelial cells show any yellowing after treatment with chromate

solutions" (Shipley and Wislocki) and Wiechowski, who studied some Bohemian toads, was unable to obtain epinephrin from their poison glands although they are chromaffin. Senso, a Chinese drug derived from a toad skin, contains a substance which is either epinephrin or a compound closely allied to it (Shimizu).

As in the case of *Bufo agua,* a toxic digitalis-like compound seems to be associated with epinephrin, so Gunn thinks the effects of cobra venom on the heart and blood vessels resemble those of epinephrin. Extracts of skin give Ehrmann's pupillary reaction on the frog eye, but do not raise the blood pressure, or give the iron reaction (Meirowski). Saline extracts of the spleen raise the blood pressure, but epinephrin has not been even thought of in this connection (Miller and Miller). Extracts of spleen give a yellow reaction with iron chlorid. Extracts of shark sex glands exert a pressor action in dogs (Brown and Joseph).

Using extracts of pituitary gland Watanabe and I obtained a vasomotor reversal in cats such as Dale reported from epinephrin after ergotoxin and argued that either epinephrin or a compound similar to it was present in that gland, but the color reactions we obtained and which resembled those from epinephrin were probably due to associated compounds and the evidence at hand shows that as I purify the pressor compound it yields no iron reaction.

Roaf and Nierenstein believe that in the mantle of *Purpura lapillus* there is a substance which is allied to epinephrin as extracts of it give the iron reaction and raise the blood pressure, and Roaf points out that in the mantle is a black streak, which stains with chromium salts, from which this compound is probably derived.

The striking action of epinephrin and its isolation has diverted attention from other constituents of the medulla, which demand study.

Chemistry of Suprarenal Cortex

It was shown that some extracts of suprarenal glands will cause a fall in blood pressure (Metzger), and this fall has been attributed mainly to cholin or its derivatives. The circulatory depressants histamin and acetyl cholin have not been looked for. Cholin has been shown to be present in the suprarenal glands, especially in their cortex (Hunt, Lohman Modrakowski).

Boruttau claimed that the side chain in epinephrin may be part of a cholin nucleus, and Borberg suggests how epinephrin might be derived, by splitting off a methyl group, from a theoretical "pro-adrenalin," which might be a modified combination of neurin and pyrocatechol. Neurin is chemically closely related to cholin. As cholin on decomposition yields hydroxy-ethyl-amin the presence of the latter in the suprarenals might be expected, at least under certain conditions.

From a study of gold and platinum precipitates, Marino-Zuco claimed to have proved the presence of neurin in these glands, but did not trace all of their toxicity to it. From a study of his lead precipitates, Marino-Zuco believed that various phosphoric acids, especially glycerophosphoric, were present, but was unable to isolate them. When neurin was mixed with these acid products, the toxicity of his mixtures corresponded to that of the original extracts and as this toxicity was lost on treatment with an acid, he believed that it was due to a phosphoric acid ester of neurin (Guarnieri and Marino-Zuco). However, it is well to remember that formerly what was called neurin was confused with cholin (Dybkowski), and later Oliver and Schäfer found that the toxic symptoms from suprarenal extracts were different from those produced by neurin, but Lohmann seems to have shown the presence of at least small amounts of neurin in the cortex of these glands.

In 1897, Metzger extracted ground-up suprarenal glands with dilute tartaric acid, concentrated on the water bath and evaporated to dryness with pumice stone. The pulverized mass, on extraction with ether, yielded a substance which gave weak suprarenal reactions, but did not reduce gold chlorid. However, crystals were found on the walls of the flask, which he said gave the iron-chlorid reaction and reduced gold. These crystals resembled leucin and exerted a pressor action. This work has not yet been corroborated.

After dehydrating the desiccated cortex with sodium phosphate, Voegtlin and Macht, by extraction with anhydrous chloroform, obtained crystalline platelets, which melted at about 50° C. These exerted a vasoconstrictor action on frog blood-vessels and a digitalis-like action on the heart.

Years ago, I tried on suprarenal extracts the method which I had used for extracting a pressor compound from an American mistletoe, i. e., dehydrating and alkalinizing an aqueous extract with a large excess of calcined magnesium oxid, then shaking with anhydrous ether and precipitating with an ethereal solution of oxalic acid. This method yielded a white precipitate which, in the amounts used, produced no noticeable rise in the blood pressure of dogs and was not studied further.

Microscopists have called attention to droplets in the suprarenal cortex some of which, unlike fats, are soluble in chloroform, or oil of bergamot after previous treatment with osmic acid (Rahl), and unlike fats are doubly refractile (anisotropic) (Kaiserling and Orgler). Some do not stain black with osmic acid (Alexander), some, at least, do not dissolve in alkalies (Moers), hence have been grouped under the name lipoids. The term lipoid must necessarily be rather indefinite and embrace a number of ill defined substances.

Stearic and palmitic acids, the phosphatid, sphingomyelin and the phosphorus-free galactosid, phrenosin, have been obtained from the cortex

by Rosenheim and Tebb and they believe the anisotropic substances in the cortex to consist of free stearic and other fatty acids with cholesterin esters, with some sphingomyelin (Rosenheim and Tebb).

According to Aschoff, doubly refractive droplets can be formed by lecithin and phosphatids, oleates, cholesterol esters and cholesterol, when dissolved in phosphatids, fatty acids, etc.

Biedl believes that cholesterin also exists in the cortex as a carnaubic acid ester (Biedl, 1913, ii, 61). However, the actual existence of a "carnaubic acid" has been questioned.

In dry human suprarenal glands Wells found 36.3 per cent of material soluble in ether of which 22.06 per cent was cholesterol and 33 per cent was called lecithin, i. e., 11.8 per cent of the dried tissue, but the report does not state that lecithin was isolated. Usually the extract of the total phosphatids is called lecithin and it is admitted that our chemical knowledge of what is called lecithin is very meagre (Maclean, Mulon; Bernard, Bigart and Labbé). Alexander states that outside of the central nervous system no organ contains as much lecithin as the suprarenals.

Lecithin easily breaks into glycerophosphoric acid and cholin. Lohmann believes that cholin does not exist as such in the glands, but that it is set free by chemical agents, as the methods used for isolating cholin are such as would free cholin from combination.

The lipins of the cortex are claimed by Borberg to contain little or no neutral fat (fatty acid triglycerids) but palmitin and stearin were believed to be present by Arnold.

What was formerly called myelin and which was reported to be present in the cortex (Virchow) is now believed to be a mixture of lipins, especially of cholesterol esters.

Kephalin is believed to be present (Biedl). Orgler claimed the presence of a protagon-like substance, but protagon is now believed to be a mixture of cerebrosids, etc.

Since the cortex seems to be essential to life and the lipoids compose such a large part of it they deserve much attention and physiologic activity is attributed to them (Iscovesco). Unfortunately we have very slight and very inaccurate knowledge of the chemical constituents of the cortex.

Cramer (1920) points out that the lipoids do not represent the internal secretion of the cortex as they are not formed in the cortex but are taken up by it from the outside, hence the cortex is a channel by which they pass to their destination. Cramer claims that the disappearance of lipoids from the cortex is always accompanied by a paralysis of the gland.

From the suprarenal glands Manasse isolated a mixture much like, or identical with, what Drechsel had previously obtained from livers and which he had named jecorin. For a long time jecorin was considered

to be a pure compound and to consist of C, H, N, S, P, Na, but some more recent work would indicate that it is really a mixture of kephalin with inorganic salts and various organic substances, cerebrosids, sugar, etc. (Maclean). The work of Meyer and Terroine indicates it to be an absorption compound, which can be made from acid albumin, lecithin and glucose in acid alcohol solution.

According to Aufrecht and Dresing the whole gland yields 23.73 per cent dry residue and of this 3.77 per cent is sulphur. In the human body only the epidermis and horny structures gave such high S content. These authors thought the suprarenal glands might have some relation to S metabolism.

No distinctive protein has been found in the suprarenals and these proteins have as yet received only slight attention. Nabarro claims that several nucleoproteins, globulins, etc. are present (Nabarro). Various xanthin bodies, hypoxanthin (Holm), xanthin, 1-methyl xanthin, probably epiguanin and adenin were reported by Okerblom. Jones and Whipple obtained a nucleoproteid, but it yielded no xanthin, hypoxanthin or epiguanin.

The suprarenal cortex oxidizes salicylaldehyd, but this power is lost by boiling and Jacoby(*b*) attributes the action to an aldehydase. Croftan has found that the suprarenals can exert a marked diastatic action and attributes it to a ferment.

The General Physiology and Experimental Pathology of the Suprarenal Glands . . . . . *Frank A. Hartman*

Introduction—Acute Suprarenal Insufficiency—Results of Suprarenal Extirpation—Compensatory Hypertrophy of Suprarenal Tissue—Differential Effects of Extirpation of each Component of the Suprarenal—Symptoms of Suprarenal Insufficiency—Muscular Asthenia—Possible Accumulation of Toxins in the Body—Altered Composition of the Blood—Reduction in Metabolism—Hypoglycemia—Changes in Respiration—Pigmentation—Gastro-intestinal Symptoms—Conditions in the Autonomic Nervous System—Postmortem Findings in Suprarenal Insufficiency—Chronic Suprarenal Insufficiency—Response to Toxins—Fatigue Effects—Suprarenal Changes Following Severe Burns—Response of the Suprarenal in Pregnancy—Reaction to Cold—Effect of Cholesterol Feeding—Influence of Diet on the Suprarenals—Effect of Inanition on the Suprarenals—Physiology of the Suprarenal Cortex—Relation of Suprarenals to Growth.

The General Physiology and Experimental Pathology of the Suprarenal Glands

FRANK A. HARTMAN

BUFFALO

Introduction

Among all of the ductless glands there are none more important than the suprarenals. This is shown by the deficiencies of pathological and of experimental origin. Depriving an animal of its suprarenals is usually tantamount to depriving it of its life. This is true in spite of the fact that in most animals both chromaphil and cortical tissue are commonly present outside of the suprarenal glands proper. We must assume therefore that this accessory tissue is inadequate alone. On these grounds we are justified in ascribing to the suprarenal glands the chief rôle among the whole mass of chromaphil and cortical tissues. However, in emphasizing the function of the larger structure we must not ignore the accessory tissue.

Since the time of Addison investigators of many countries have attempted to produce experimentally the syndrome which he in so masterly a way described. None have really succeeded, due no doubt largely to the fact that no satisfactory method has been found of gradually reducing suprarenal function. In most instances the animal has been suddenly deprived of the major part of its active suprarenal tissue in one, or, at the most, two steps. This permits neither time for readjustment nor time for the appearance of chronic symptoms but merely demonstrates whether the suprarenals are essential to life.

Acute Suprarenal Insufficiency

Results of Suprarenal Extirpation.—Immediately following the description of Addison's(*b*) disease Brown-Séquard(*a*) studied the effect of the removal of the suprarenal glands in rabbits, dogs, cats, guinea pigs and rats. He observed that an animal died within a few hours or at most one or two days after being deprived of its glands.

A number of workers immediately questioned suprarenal insufficiency as the cause of death. Gratiolet found that removal of the right gland only (guinea-pig) produced the same symptoms as the removal of both glands. Because of the hepatitis and peritonitis which he observed in his animals he came to the conclusion that the loss of the gland was not the primary cause but rather it was the injury to the liver and other structures which was responsible for the symptomatology observed.

Philipeaux in the same volume of the *Comptes rendus de l'Académie des Sciences* in which the foregoing observations were published concluded as a result of extirpation experiments with the rat that the suprarenals are not essential to life. Although removal of both glands at the same operation caused death in one or two days, no ill effects were produced in some animals if each gland was removed at a different time with several days intervening. The glands were removed by the lumbar route. Many others working with different animals came to similar conclusions.

After several years, during which no work was done toward a solution of this problem, Nothnagel(*a*) revived interest by trying to produce a true Addison's disease through lesions of the glands. He hoped to induce a chronic inflammation. At this time, however, no work was done to settle the important question as to whether the suprarenals are vital to life.

In 1891-92 Abelous and Langlois(*a*)(*b*)(*c*) clearly demonstrated the vital importance of the suprarenals. Removal of one gland was without effect while destruction of both caused death in two or three days in the frog and in less time in the case of the guinea pig. They observed that death was preceded by muscular paralysis and slow respiration.

Among the numerous investigators studying the problem during this period were Hultgren and Andersson(*a*) whose careful work deserves special notice. They found in cats that one-sided extirpation did not produce death and that the removal of both glands in two stages prolonged the life of the animal to an average of 130 hours in cats (11 cases), whereas when both were removed at one operation the average length of life was 68 hours. Rabbits might live as long as five or six days after removal of both suprarenals. Animals, previously castrated, survived double capsulectomy many hours longer than those not castrated, in some cases twice as long.

In recounting the steps which established the importance of the suprarenals we must include the extensive researches of Strehl and Weiss. They operated upon more than one hundred animals, the capsules being reached in most instances through an incision along the linea alba. In a few cases, however, the approach was made through the lumbar pathway. The time of survival after double capsulectomy was compared in several different species. Guinea pigs lived four to nine hours after removal of the glands while dogs sometimes survived as long as one hun-

dred and thirty-eight hours. Cats, rabbits, rats, mice and frogs lived usually a day or two.

Still greater improvement in technique has established beyond a doubt that the symptoms produced are due to a loss of the glands and not to trauma incident to the operation. Biedl's method of suprarenal extirpation offers unquestionably the best means of avoiding complications due directly to the operation. He first dislodged the suprarenals in a dorsal direction through lumbar incisions. Leaving the glands attached by means of the blood vessels he sewed them in between the skin and the musculature. No ill effects were observed. Three or four days later the glands were exposed by cutting through the skin and then removed after the blood vessels were ligated. The results of his experiments confirmed the conclusions that the suprarenals are essential to life.

One of the greatest stumbling blocks in the solution of the suprarenal problem has been the work on the rat. It had been shown that some individuals could survive extirpation of both glands. This raised the suspicion in the minds of many that perhaps these structures are not so important after all.

This question of the value of the suprarenal in the life of a rat was revived by the work of Boinet(*a*). He found that six out of forty-eight rats survived longer than five months and were in perfect health after double epinephrectomy. In answer to the criticism of Abelous and Langlois that these survivals might be explained by the presence of accessory suprarenal tissue, Boinet(*c*) removed both suprarenals and such accessory suprarenals as he could find in twelve rats. Seven animals recovered. He claimed, therefore, that the rôle of accessory tissue in decapsulated rats was exaggerated.

Boinet stated that he removed the supplementary glands situated at the junction of the renal veins or along the border of the posterior surface of the kidneys. However, Wiesel has found accessory cortical bodies between the testicles and the lower pole of the epididymis. These evidently were not excised by Boinet and supposedly account for his negative results. At any rate the rat does not give the clear cut evidence which we desire. Those animals which do survive double capsulectomy must possess a larger amount of accessory tissue than usual. Occasionally other species survive a similar operation but the percentage of subjects that survive seems to be related to the proportion of accessory tissue present. The guinea pig, on the other hand, which rarely ever (Velich(*c*)) possess accessory cortical tissue seldom survives double epinephrectomy.

Compensatory Hypertrophy of Suprarenal Tissue.—Not only does the presence of accessory tissue play an important part in the maintenance of life after removal of suprarenal tissue but the hypertrophy of this tissue as well as of portions of the suprarenal left *in situ* may lead to permanent recovery, or at least postpone the fatal result.

It is well known that when one suprarenal is removed the other hypertrophies. Stilling(*a*) long ago demonstrated that the remaining gland might double its weight. Even a small piece of a suprarenal may grow to considerable size after partial excision of the gland. H. and A. Cristiani(*a*) actually measured such fragments at the time of operation. In the course of several months they found in some instances that these pieces had grown to more than half the size of a normal gland. Moussu and Le Play cite a case in which one suprarenal was removed and four months later the greater part of the other gland was excised. The animal (dog) recovered and remained in perfect health. One year later when the animal was killed the suprarenal fragment was found to have increased to normal size.

Hypertrophy having been shown to follow partial ablation the next question was to determine whether both medulla and cortex take part in this reaction. Canalis thought that it was confined to the cortex. The findings of Labzine also confirmed this. Elliott and Tuckett, however, state that hypertrophy may occur in either medulla or cortex. In a cat suckling kittens they found an increase in the number of medullary cells. Furthermore they observed in a guinea pig from which one gland had been removed, that the medullary cells were largely responsible for the increased growth in the compensating gland. In the rabbit, however, compensatory cortical growth was much more rapid than in the medulla. It is impossible to say which is the more important, medullary or cortical hypertrophy, yet there is considerable evidence that indicates the latter. For example, it is said that the enlargement to meet the strain of pregnancy as well as the increase incident to infection is largely in the cortex.

Differential Effects of Extirpation of Each Component of the Suprarenal.—Are both cortex and medulla essential to life? Theoretically this question should be most easily answered in the fishes for here the two tissues corresponding to the cortex and the medulla of the mammalian suprarenal are separate.

Biedl(*g*) removed the interrenal cortical body in twelve specimens of Scyllium. It consists of a long band lying between the kidneys and extending toward the cranium. Two animals died in ten days. In these the interrenal body had been completely removed. The other fish were killed at the end of three weeks. Remnants of interrenal tissue were found in them.

In the Raiidæ it is possible to remove the interrenal tissue with more certainty. In thirty-two individuals belonging to the Genera Torpedo and Raia, Biedl succeeded in removing all traces of the interrenal tissue from twenty-seven. Although the other five did not die they showed symptoms of interrenal insufficiency. On the other hand the remaining tissue appeared to be hypertrophied. The animals from which

the interrenal tissue had been completely extirpated died with characteristic symptoms.

Although the results of Pettit and of Vincent(*b*)(*c*) on the Teleosts did not agree with those of Biedl, this was later accounted for by Giacomini's discovery, that in the eel, in addition to the body of Stannius and neighboring interrenal tissue, there is found an anterior cranial mass of interrenal tissue. This had been overlooked by Vincent.

In mammals Biedl(*g*) claims that he was able to remove the cortex, leaving the medulla intact. Death followed. Such an operation appears little better than removal of the whole gland because of the intimate vascular connection between cortex and medulla. However, because of the results with fish we may conclude that the cortex is essential for life.

As regards the medulla the answer is more difficult. H. and A. Cristiani(*a*), in their attempts to determine the minimal suprarenal tissue necessary for life, found from histological examination that only those animals survived which possessed a small portion of functioning medullary tissue. Small pieces with medullary substance permitted life while relatively large pieces in good condition but without medullary substance were not sufficient to preserve life.

But more recently Wheeler and Vincent have destroyed all of the medullary tissue in the two glands by removal of one, amputation of half of the other and cauterization of the medulla in the remaining half. They state that in several instances where the whole or practically the whole of the medulla has been destroyed the animal has survived without symptoms. The animals were kept for three or four weeks, the gland tissue being examined microscopically for medullary tissue at the conclusion of the experiment. This work indicates that the medulla is not essential or at least from all of the evidence available we may conclude that of the two tissues the cortex is the more important. Extrasuprarenal chromaphil tissue might function sufficiently to replace the loss of medullary tissue; but even so, it follows that the medullary tissue is not essential to life.

Symptoms of Suprarenal Insufficiency.—The syndrome of experimental suprarenal insufficiency develops rapidly in a large proportion of the cases. Usually the first severe symptoms occur only a few hours before death. Therefore it is not surprising that the picture is not identical with that of Addison's disease, which is due no doubt to slowly developed suprarenal insufficiency.

Of the very many accounts of the general symptoms following epinephrectomy that of Elliott(*f*) is one of the best. His experiments were made on the cat. In a series of 21 animals, both glands were removed at the same operation, nineteen dying within 48 hours. In another series of twenty-five cats the glands were removed in two stages, three weeks to nine months apart. Survival in this series ranged from six to twenty-

three days after excision of the second gland. The second gland (cortex) was found hypertrophied in some. The splanchnic nerves were carefully avoided in all operations. The symptoms were very similar in both series. The animals lost appetite, finally refusing to eat meat and taking only small amounts of milk. The weight decreased, those surviving long becoming very thin. A characteristic weakness developed just before death. The animal found difficulty in walking and soon would lie with belly on the ground and limbs relaxed. It might become so feeble that it lay on its side with limp legs and tail extended. Yet in spite of this weakness there was full possession of the power of the skeletal muscles because even a moribund cat could be stimulated to normal muscular activity. The blood pressure of the dying animal was extremely low but no mention was made of the time at which this fall in blood pressure first occurred. Due to the low pressure the respirations became labored. The heart mechanism appeared to be unaltered judging from a series of electrocardiograms taken daily until the final collapse (one animal).

Artificial heat had to be furnished in the later stages to prevent a fall in the rectal temperature. Emotionally no annoyance was shown, the cat purring until the final collapse.

The observations of Moore and Purinton(*d*) are of special interest because they watched their animals (cats) day and night after removal of the second gland, temperature, respiration and other symptoms being noted at short intervals. They describe pyrexia during the first few hours. Muscular asthenia developed later and increased as time went on. The respiratory rhythm became markedly increased but later the respiration began to fail and finally caused death. Muscular twitchings over the body appeared a few hours before death.

These investigators also removed the suprarenals from four goats, three dying as a result. The principal symptoms in these animals were asthenia and shallow respiration. It is typical of animals dying from excision of the suprarenals that the onset of serious symptoms is usually sudden, occurring but a few hours before death. Marshall and Davis say that coma and convulsions usually appeared in their cases about thirty minutes before death.

Muscular Asthenia.—All seem to be agreed that the most characteristic symptom in suprarenal insufficiency is muscular asthenia. Such weakness is strikingly illustrated by the observation of Strehl and Weiss that cats which were very wild and pugnacious before became quite apathetic after capsulectomy.

In this connection we should point out that it has been very definitely shown that the animals deprived of both suprarenals become fatigued much more readily than do normal animals. The work of Albanese(*a*) on frogs and rabbits has contributed much toward an understanding of this problem. Their frogs were fatigued to the point of paralysis of the volun-

tary muscles by stimulation from an induction coil. Normal animals recovered while decapsulated animals died. The symptoms preceding death were similar to those present in decapsulated animals which were allowed to die without stimulation, stimulation merely hastening their appearance.

In the case of rabbits each animal served as its own control. The strength and duration of the stimulation necessary to produce fatigue were determined the day before decapsulation. Four or five hours after the decapsulation, the animal was stimulated in a similar manner a few minutes at a time. He recovered from the fatigue much more slowly after each trial. Although immediately following decapsulation the animal appeared quite normal, after fatigue from the stimulation prostration soon occurred, the temperature fell, respiration became superficial and finally convulsions resulted followed by death. Here again stimulation hastened the onset of the characteristic symptoms which develop in decapsulated animals. On the other hand rabbits which had gone through similar operations except that the suprarenals were left intact, recovered from the fatigue as did normal animals. These results led Albanese to believe that the suprarenals are essential for the removal of the toxic products of fatigue.

Possible Accumulation of Toxins in the Body.—If removal of toxic substances from the blood is a function of the suprarenals it should be possible to find such substances in the circulating blood of the decapsulated animals.

Abelous and Langlois(*a*)(*b*) injected blood from a frog which had just died from decapsulation into a normal frog. Breathing became slower and the muscles weakened but after several minutes the animal recovered. A similar injection into a frog decapsulated one hour previously caused complete paralysis in twenty minutes, while blood of a freshly decapsulated frog was without result. The same observers(*c*) later reported that the blood of guinea-pigs dying after suprarenal extirpation was fatal to frogs.

Injection of an alcoholic extract of the muscle of frogs(*f*) which had died of capsulectomy produced immediately the grave symptoms of suprarenal insufficiency in decapsulated frogs. Extracts of tetanized muscle which had been deprived of its circulation produced like effects upon injection into decapsulated frogs. If the decapsulation had not been complete the effects were not so severe.

The work of Levin suggests that abnormal substances are formed or collect in the blood. He performed some experiments in which the blood taken from decapsulated cats or dogs five hours after the operation was injected into normal animals of the same species. He obtained a rise in blood pressure which was sometimes preceded by a slight fall. He obtained no effect from the injection of the blood from normal animals similary prepared. The difference in the reaction was attributed to some substance contained in the blood of decapsulated animals but absent in nor-

mal blood. The apparent toxemia of decapsulation may be due to two factors, viz., a lowered resistance to poisons and an accumulation of harmful substances in the blood.

Boinet's(e)(g) investigations seem to show a lowered resistance. He found that doubly decapsulated rats were less able to withstand the injection of toxic substances than were normal subjects. Some have suggested that the suprarenal has a detoxicating or toxin-neutralizing function. Although the evidence which supports this idea is mainly of an indirect nature Myers has found that the mixing of cobra venom with an emulsion of suprarenal cortex destroys its toxicity.

Altered Composition of the Blood.—Experiments in relation to toxemia indicate that the composition of the blood becomes changed after double capsulectomy. Gradinescu reported that the plasma became more concentrated, while Donath definitely stated that there was an increase of about five per cent in the solids.

Changes in the concentration of specific substances in the blood have been noted by many. Porak and Chabanier found an increase in the blood urea of seven rabbits from which both suprarenals had been removed. This, however, might have been due incidentally to the moribund condition of the animals for they lived only from eight to twelve hours after the operation.

Marshall and Davis have shown that certain products of metabolism tend to accumulate in the blood of decapsulated animals before they reach the moribund condition. By operating through the lumbar pathway in two stages they succeeded in preserving the life of their cats for periods of time ranging from one to seven days or an average of three and one-half days (16 animals) after the second operation.

They found that the urea concentration in the blood rose to about twice normal where it remained until shortly before death when it again rose. This was due to the decreased functioning power of the kidneys for it was shown that they excreted very slowly urea and creatinin injected into the blood. Inasmuch as the decreased efficiency of the kidneys in the animals deprived of their capsules may occur with a normal blood pressure and while the animals are in an excellent physical condition Marshall and Davis have suggested that the suprarenal produces some substance which is necessary for normal kidney function.

It has been pointed out by Whipple and Christman that the excretory power of the liver is reduced by removal of three-fourths or more of the suprarenals. They found that phthalein injections were excreted much more slowly in such cases.

Reduction in Metabolism.—Metabolism becomes much reduced during suprarenal deficiency. This is indicated by the fall in temperature which in later stages becomes so marked that raising the surrounding temperature to 50° C. does not restore it to normal (Gautrelet and Thomas).

The temperature fall does not occur during the early hours of the experiment if Biedl's dislocation method is employed. He says that the temperature begins to drop about 48 hours before death at the time when asthenia appears. There is a gradual reduction until just before death when the fall becomes more abrupt (Hultgren and Andersson).

Schwartz found a decrease in the metabolism after double epinephrectomy. Gradinescu determined the oxygen and carbon dioxid exchange and likewise found a decrease. The results of the latter are illustrated by results taken from his table:

Respiratory Exchange in Decapsulated Animals (Gradinescu).

Before Operation			After Removal of Both Suprarenals			
Rectal Temp.	O_2 used per hr. per kgm.	CO_2 expired per hr. per kgm.	Rectal Temp.	O_2 used per hr. per kgm.	CO_2 expired per hr. per kgm.	Hrs. after removal
Dog ..38°C.	954.5 cc.	939 cc.	38°C.	547.2 cc.	449.2 cc.	17
Cat	556.8	554.4	37°C.	684	608	9
			38	482	509	33
			32.5	250.3	223	47
			30	69	210	53

By the use of the calorimeter Gradinescu determined the amount of heat production in enpinephrectomized animals.

Heat Production after Double Epinephrectomy. (After Gradinescu.)

Hrs. in Calorimeter		Calories per kgm. per hr. normal	Calories per kgm. per hr. after $CHCl_3$ narcosis	Calories per kgm. per hr. after extirpation	Survival in hrs.	Hours after extirpation
Dog	1	3.17	2.98	2.53	14	2
3.35	2	3.17	2.91	2.53		
kgm.	3	3.00	2.80	2.26		
	4	2.71	2.90	2.15		
	5	2.98	2.80	2.44		
	1			2.24		9
	2			2.36		
	3			2.30		
	4			1.80		
	5			1.30		
	6			1.01		
Dog	1	2.91	3.30	3.15	120	3
5.55	2	2.73	3.50	3.15		
kgm.	3	2.73	3.35	3.30		
	4	3.30	3.42	3.30		
	5	2.73	3.35	3.10		
				3.00		24
				3.15		
				3.64		48
				2.70		94
				2.76		106
				2.01		112
				1.02		114

The after-effects of chloroform were determined so that it could be taken into account following the operation. Excerpts from his table are given. There comes a time when there is a reduction in the amount of heat produced as would be expected from the subnormal temperature which develops. Muscular asthenia is no doubt an important factor in producing this condition.

It is also to be noted that those animals which show a decided reduction in heat production after the operation live but a few hours. On the other hand, animals which survive for days, do not present marked reduction until a few hours before death.

Gradinescu's results have recently been confirmed by Aub, Forman and Bright.

Hypoglycemia.—A further indication of metabolic disturbance is the lowering of the sugar content of the blood. This reduction is not due to operative shock because animals similarly treated but without excision of the suprarenals do not show it (Porges). An example of the blood sugar decrease is seen in the decapsulated dog of Bierry and Malloizel. Before the operation the sugar content was 1.2 gm. to 1000 gm. of blood. After excision of the capsules it had fallen to 0.8 gm.

Experimental glycosurias and hyperglycemias are not so readily produced in decapsulated animals as in normals. Mayer(*b*) found that *piqûre* does not produce glycosuria in dogs and rabbits which lack the suprarenals. Gautrelet and Thomas(*c*) failed to cause glycosuria by stimulation of the splanchnic nerves in decapsulated animals. Epinephrin produced a smaller increase in the blood sugar than normal. The resulting glycosuria was also smaller. Kahn(*f*) could not obtain CO or diuretin hyperglycemia in a decapsulated rabbit, although he found that the liver glycogen was normal.

The reduction in the quantity of circulating carbohydrate might be due to the smaller amount ingested as a result of decreased appetite. If Schwartz's observation is correct it seems that there is less glycogen stored in the body. He found glycogen absent in the liver of a decapsulated mouse. That would account for the failure of epinephrin and other substances to cause the usual hyperglycemia.

Changes in Respiration.—One of the late symptoms of suprarenal insufficiency is the progressive failure of the respiration. In such animals polypnea is not caused so easily by exposure to high temperatures. We may cite as typical one of the experiments of Gautrelet and Thomas(*d*). A rabbit whose respiratory rate was 135 per minute showed an increase to 150 per minute immediately following double capsulectomy. Two hours later this had been reduced to 100 per minute. At two and one-half hours it had become 56 per minute. The surrounding temperature was then raised to 42° C. but there was no increase in the rate, the rectal temperature remaining at 33° C. However, elevation of the neighboring

temperature to 49° C. for forty minutes raised the rectal temperature to 36° C. and increased the respiration to 130 per minute. The animal died a few minutes later, death probably being hastened by the high temperature.

Because morphin had been used during the operation in many of these experiments we thought that it might possibly have been the cause of the sluggish respiratory reaction. Therefore we [1] repeated the observation on a cat in which ether only was used as the anesthetic. One gland was removed and a large proportion of the circulation to the other was tied off. Before the operation the respirations numbered sixty to seventy-five per minute. Nineteen hours afterward respirations had been reduced to twenty-eight per minute. Forty-eight hours after, the pulse rate had increased from 180 to 240 per minute. The cat could walk fairly well but it chose to lie close to a hot radiator all of the time. Mental alertness was lacking.

Five days after the operation the rectal temperature was 34.8° C., the heart beat was 150 per minute; it was determined by a stethoscope as it was scarcely palpable. The gums were bloodless. The animal could stand and walk about but was very weak. The respirations were now twenty-four per minute. Placing it in a temperature of 40° C. for five minutes produced no change in respiration, nor did exposure for the same length of time at 44° C. produce any effect. Death occurred a few hours later.

Perhaps these respiratory effects are due to a partial paralysis of the respiratory center. It is well known that epinephrin injections influence the respiratory center. Yet Gautrelet and Thomas observed that the respiratory acceleration which results from the injection of epinephrin, was suppressed.

Failure of respiration may be the cause of death from suprarenal insufficiency for just before the final collapse the respirations are greatly reduced. In the dog they may occur at the rate of five or six per minute, while in the rabbit the rate may become as slow as twenty per minute (Gautrelet and Thomas).

Pigmentation.—The pigmentation which appears in Addison's disease fails to develop in most cases of suprarenal insufficiency. Earlier investigators describe many instances of pigmentation. In fact Brown-Séquard(*a*) believed death from capsulatectomy to be due to an accumulation of pigments in the blood. Among those who have described pigmentation are Nothnagel(*a*) who noticed spots on the mucous membrane in three decapsulated animals out of 153, and Tizzoni who observed pigmentation in a larger proportion of such animals. The development of tiny gray patches in regions where the skin has been shaved has been described in suprarenal insufficiency by F. and S. Marino-Zuco. These findings have failed of

[1] Unpublished results of Eisenberger and Hartman.

confirmation at the hands of later workers with the exception of Boinet(*a*), who not only describes pigmentation but says that hematoidin-like granules are found in the blood of rats which survived suprarenal extirpation a long time.

Although it was carefully sought for, Langlois(*f*) never discovered, in all of his experiments, any clear case of pigmentation. The rare modifications observed either in the mucous membranes or the hairs were no more marked than in normal animals. Harley(*b*) and Stilling have likewise never seen pigmentation develop in experimental suprarenal insufficiency.

If one examines a normal animal closely, he notices that there are frequently many variations in color of the skin or mucous membrane which might easily be attributed to excessive pigment formation had the suprarenals been removed. Therefore until observations are controlled by actually mapping the location and intensity of such variation before capsulectomy, all pigmentation described in experimental suprarenal insufficiency must be doubted.

Gastro-intestinal Symptoms.—Changes are produced in the alimentary canal by epinephrectomy. Undisputed proof of this is found in the gastric ulcers which have been frequently described in decapsulated animals (Freidmann, Elliott(*f*), Mann). In this connection it should be mentioned that Goodman has described pathological changes in the suprarenals of five cases of gastro-duodenal ulcer. Diarrhea, although rare, has occasionally been described (Elliott and Tuckett). We have also noted it in rare instances.

These changes may contribute to the loss of appetite which is prevalent in the later stages of suprarenal insufficiency. The loss of appetite together with a possible reduction in digestion and absorption might well be the cause of loss in weight of the animal. The cause of the changes in the alimentary canal is at present unknown.

Conditions in the Autonomic Nervous System.—Elliott suggested that the symptoms exhibited after removal of the suprarenals are due to a hindrance of the activities of tissues especially innervated by the sympathetic nervous system. They lost tone and might fail to respond to electrical stimulation of the nerves. So they might fail to respond to the normal physiological impulses. Thus blood pressure falls progressively and the heart beat weakens. He found that under such conditions nicotin was unable to effect a rise in blood pressure even if atropin were given to prevent inhibition of the heart. Neither pituitary extract nor barium chlorid seemed to have any effect upon the blood vessels, but epinephrin still produced a rise in blood pressure almost as great as normal. Such vasomotor paralysis was found only in very weak and moribund cats. It was suggested that such a deficiency might be due to the absence of epinephrin. In other words, that this substance was necessary for the maintenance of sympathetic irritability.

Gautrelet and Thomas(*e*) claim that the excitability of the sympathetic, especially the abdominal, becomes very much lowered a few hours after epinephrectomy. They used as criteria the pupillary response from stimulation of the central end of the cut vago-sympathetic nerve trunk and the blood pressure response from sciatic and splanchnic stimulation. Stimulation of the depressor nerve in the decapsulated rabbit produced no effect. (Blood pressure was 50 mm. Hg.) During the stage when the heart becomes weak and the blood pressure becomes low, the vagus was found to be less irritable than normal. They attributed the rapid heart action in part to a loss in the vagus function because stimuli which formerly stopped the heart merely decreased the rate after decapsulation.

After the removal of both suprarenals in the rabbit Roger(*a*), on the other hand, obtained greater inhibition of the heart by vagus stimulation than is produced normally. Cardiac escape was later than usual and the secondary rise of blood pressure was absent. Continuous injection of an amount of epinephrin which produced no apparent effect on blood pressure caused decapsulated animals to respond as do normal animals. Roger believes that the suprarenal glands are responsible for the diminishing effects of repeated vagal stimulations.

Hoskins and Wheelon have tested the sympathetic irritability hypothesis by studying the effects of afferent nerve stimulation and of injections of epinephrin and nicotin, upon blood pressure. These were tried four to nine hours after removal of both suprarenals in the dog. Normal responses were obtained but this may have been due to an insufficient time for the development of symptoms.

More to the point were the experiments of Hoskins(*g*) which indicated that sympathetic failure was not a primary feature of the syndrome. Even when a decapsulated animal had become so weak that it could scarcely stand, its vasomotor system responds to stimulation perfectly well. Therefore sympathetic failure is secondary, being preceded by muscular and cardiac weakness.

Yet it does appear from the numerous observations which indicate a lessened irritability of portions of the autonomic nervous system, that this is a frequent symptom in the advanced stage of suprarenal insufficiency. More evidence is desirable.

Post-mortem Findings in Suprarenal Insufficiency

The most important post-mortem finding following suprarenal insufficiency is perhaps that sometimes occurring in the central nervous system. Ettlinger and Nageotte have found vacuolization of the nerve cells in animals which died a few hours after the operation (dog), while similar changes failed to appear in control animals. The modification

of the medulla was the most characteristic, short fissures surrounding irregular fragments occurring in the protoplasm of the cell. The superficial zone of the cerebral cortex was also vacuolated. The authors suggest that these vacuoles are due to autointoxication.

Donetti has also described changes in the central nervous system of decapsulated guinea pigs and rabbits. In his animals also the bulb was most affected.

Congestion of the blood vessels has been described in death from capsulectomy. Boinet(*a*) described thirty-five cases of pulmonary congestion out of fifty autopsies on rats. There were two cases of hemorrhage. Twenty cases showed congestion of the bulb. He was able to produce congestion of the lungs and cerebrum with or without hemorrhage in rabbits, rats and guinea pigs by the injection of extracts of muscle, viscera or blood taken from rats which had died of decapsulation. He attributed this to toxic substances.

Moore and Purinton(*c*) described cardiac thrombosis in three cats which died of capsulectomy. Death had occurred within thirty-four hours after the removal of the second gland.

These post-mortem changes certainly point to the formation of toxic products.

Chronic Suprarenal Insufficiency

We have given an account of symptoms produced in acute suprarenal insufficiency. As we have pointed out before, some of them develop so rapidly that they are difficult to follow.

Attempts to produce a chronic insufficiency are not new. Very many have tried by different means to reduce the amount of suprarenal tissue without destroying all. Nothnagel(*a*), Russo-Giliberti and Di Mattei and others employed such methods as cauterization, crushing and injection of substances into the gland. Some have sought to produce suprarenolysin and epinephrinotoxin but they have added little to our knowledge of the suprarenals further than the picture of the histological changes induced by such procedure.

Perhaps the most satisfactory method of destroying the function of a large portion of the suprarenal is by reduction of the circulation. This has been done by Martinotti in the rabbit, the suprarenal veins being occluded. He studied the histological changes which followed.

Alterations in the protoplasm and nuclei of both medullary and cortical cells was observed as early as twenty-four hours after the occlusion. The changes in the cortex varied considerably in different parts of the gland apparently as a result of differences in circulatory modification. The cells in some regions had become vacuolated and in many cases the nuclei appeared shrunken. On the other hand, no characteristic changes

were noticed in the medulla during the first twenty-four hours. Two months after the operation the suprarenal had been reduced to a yellowish-brown body of about one-tenth normal size. Connective tissue had pretty well replaced the cortex although here and there fragments of cortical cells were seen. In certain special conditions where the circulation appeared to be still preserved small groups of apparently normal cortical cells were present. These were most apt to occur in the external part of the glomerular layer. After two or three months no trace of medullary cells was to be found, connective tissue having replaced them.

The symptoms produced by ligation of the efferent suprarenal vessels has been studied by Koudintzeff. His animals survived sixteen to twenty-four days. There was a progressive increase in contractions of the hind limbs. At first the contractions were feeble and more frequent but as they became violent they were rarer apparently on account of a partial paralysis. The temperature was elevated continually. There appeared to be a general intoxication and atrophy, the animal gradually decreasing in weight. Death occurred during a convulsion. Goliakhowski's observations led him to conclude that the results from tying the suprarenal veins were the same as those from suturing the gland. He observed diarrhea, hyperexcitability, exaggerated reflexes, loss in weight; later, lowered sensibility, apathy, paralysis and gradual fall in temperature. The syndrome appeared to be similar to that of Addison's disease.

Because of the small rete of vessels connecting the suprarenals with the kidney in the cat it is possible to tie off the suprarenal veins without complete occlusion of the circulation (Fig. 4, page 401). Hartman and Blatz used these animals in an attempt to produce suprarenal insufficiency.

One animal lived forty-eight days after obstructing all exits from both suprarenals excepting the kidney rete. No noticeable symptoms developed except muscular weakness just before death. Epinephrin was present in the medulla (chromaffin reaction). Removal of one suprarenal and occlusion of the veins from the other caused death in two days in another cat. The suprarenal was found congested with blood as were also the superficial veins of the kidney on the same side.

Other experiments were tried in which only the common lumbo-adrenal vein was tied off, centrally, the vein from the lumbar muscles being left intact. An animal operated upon in this way after removal of one gland lived for 128 days. This animal developed a chronic condition which caused the appearance of characteristic symptoms. After several days the hair on the ears and face began to fall out and at forty-six days eruptions appeared on the skin of the face. A little before this a red coloration developed on the inner side of both forelegs. The cat began to cry incessantly and lost weight.

Sixty-eight days after the operation the weight had dropped from 2.50 kgm. to 2.06 kgm. The animal was not so active, largely on account of

muscular weakness because it still appeared restless and irritable. The hair was very scraggy and unkempt. The temperature (rectal) was perhaps a little high (39.1° C.) while the heart rate was normal (249 beats per minute).

A part of the weight lost was regained during the next month. Some of the strength also returned but the animal still walked with a stiff-legged gait. The fur however remained in a poor condition, the longer hair such as the vibrissæ being broken and scraggy. Then again the cat commenced to get worse, until it was reduced to 1.75 kgm. in weight at death. The day before death it appeared very much as it had for weeks. Post-mortem examination showed everything well healed. Both lipoids and epinephrin were present in the suprarenal.

More recently we have tied both lumbar and lumbo-adrenal veins on both sides in two kittens (unpublished reports of Hartman and Eisenberger). After transient symptoms of suprarenal insufficiency they began to gain in weight and appeared perfectly normal. Eighty-seven days later the right suprarenal was removed in one kitten. The gland appeared to be almost normal, the circulation apparently having been reëstablished. No marked symptoms developed until fourteen days after the second operation, when two convulsions occurred about three hours apart. Accompanying these were marked salivation and dilatation of the pupil. For three to four minutes after the seizure had passed the animal remained prostrated. Recovery would be quite complete for a few hours before the next seizure. The animal died during the night in a convulsion, as was judged from the position in which it was found. The left suprarenal appeared to be completely atrophied.

We have cited this to show how variable may be the extent of circulatory interference from tying the veins. The tiny efferent vessels may function sufficiently to prevent loss of active tissue below the danger point or again the circulation may be so completely checked that the gland dies. Moreover any intermediate stage between these two conditions is possible.

We cannot expect to find a complete analogy between the symptoms of Addison's disease and acute suprarenal insufficiency of experimental origin. In the latter we commonly find the following which are analogous: failure of appetite, muscular asthenia, emaciation and loss of weight if the survival is long, low blood pressure and weak heart in the last stage; occasionally there are evidences of gastric disturbance (ulcers and diarrhea). But so far pigmentation has never been demonstrated experimentally.

We know that Addison's disease is due to deficiency in the suprarenal function, but we have so far been unable to imitate this experimentally because of the great difficulty in producing a chronic condition.

Suprarenal Substitution

Attempts have been made to replace the substances lacking in experimental suprarenal insufficiency. Extracts have been injected, suprarenal tissue has been administered by mouth and glands have been transplanted.

Abelous and Langlois(*a*), Brown-Séquard(*b*) and Hultgren and Andersson claim to have produced temporary benefit from the injection of suprarenal extract. The last mentioned workers found that the subcutaneous injection of this extract improved the general condition and slightly relieved the asthenia.

Strehl and Weiss prolonged the life of decapsulated animals for nine hours longer than controls by the injection of suprarenal extract.

Biedl says that he has treated a large number of animals, by feeding with suprarenal tabloids previous to epinephrectomy for periods varying from a few days to several weeks, the treatment being continued after operation by means of subcutaneous injections of aqueous extract of the suprarenal. The average length of life of the animals under treatment was very little longer than that of the controls.

Mariani was unable to prolong the life of decapsulated animals with injections of suprarenal extracts of the same species. Moreover medullary or cortical extracts of a different species hastened the death of decapsulated animals.

If the absence of epinephrin is one of the factors producing the symptoms of decapsulation its injection should ameliorate the condition. Hoskins and Rowley found that such injections were of no benefit.

Suprarenal grafting has been attempted again and again.

Canalis implanted pieces of suprarenal in the kidney and found that they were absorbed.

Abelous (1892) described what he supposed to be true grafts. These were planted in normal frogs from which, after the former had healed in, the suprarenals were removed. Twelve days afterwards removal of the grafts caused the appearance of the typical deficiency syndrome. Eight out of thirty cases were successful. To be conclusive a much longer period should have elapsed for as the following experiments show these transplants are absorbed in time.

Langlois inserted fragments of the kidney with the suprarenal adhering under the skin in the dorsal lymph sac of decapsulated frogs. Such animals were found to survive somewhat longer than those frogs which were simply decapsulated. They might live five or six days. At autopsy the grafted glands were found to be partly absorbed, having in no way established connection with the circulation. Gourfein likewise found that grafts in frogs eventually disappeared (40 days).

Suprarenal grafting in mammals has been somewhat more successful, although the earlier experimenters failed.

Boinet(*a*) was unable to prolong the life of decapsulated rats by intraperitoneal grafts. Hultgren and Andersson were unsuccessful with intramuscular grafts in cats and rabbits. Strehl and Weiss tried placing the suprarenal loosely in a pocket made from the musculature of the abdominal wall or else in the liver or kidney but without success.

Poll made careful histological studies of grafted suprarenals, a majority of which were placed either under the skin or else in the muscles. Twenty-three out of fifty-four cases showed regeneration of a small part of the cortical tissue while the medullary substance entirely disappeared.

The work of H. and A. Cristiani(*b*) deserves special attention because it follows the development of the histological changes which occur in a transplanted gland. Their method consisted in removing one of the suprarenals of a rat and planting it as a whole or in pieces in the peritoneal cavity of the same animal. In from one to six days the graft had been enveloped in the omentum, to which it adhered, and the peripheral region of the cortex had begun to regenerate where new vessels were penetrating. Regeneration advanced more and more into the necrosed portion being preceded by new vessels. The medullary layer entirely disappeared being replaced by cicatricial tissue.

In whole glands the failure of the medulla to regenerate might be due to the long period elapsing before the interior of the transplant is reached. However it was found that division of the gland so that medullary cells could have an early opportunity to become vascularized, made no difference although in a few instances the observers appeared to find regeneration of some medullary tissue; but they were never able to obtain the typical reaction with potassium dichromate.

In spite of the apparently satisfactory regeneration of the cortex, the grafts were never able to replace the function of the normal suprarenals for the removal of the latter caused death just as in animals not possessing the grafts.

It has been shown that grafted cortical tissue may survive for a long period. Stilling(*c*)(*d*) has found typical cortical tissue in suprarenal transplants in the testicle of the rabbit after three years. v. Haberer obtained dislocation grafts which functioned successfully. The gland with its vascular pedicle intact was implanted in the kidney. In time the original pedicle completely degenerated while a new vascular system developed from the kidney. In seventeen dogs both glands were transplanted at different intervals. Five animals survived this operation for years without the development of symptoms of insufficiency. Histologically the medulla was shown to have regenerated.

These authors found that the region of the suprarenal near the vascular stalk remained alive and served as the starting point for the re-

generation of new tissue, regeneration gradually spreading through the necrosed region. It took about five months for the stabilization of degeneration and regeneration.

Strictly speaking these experiments do not deal with true grafts. Moreover no practical application could ever be made of such an operation.

The really valid examples of successful grafts were those obtained by Busch, Leonard and Wright. A sagittal third of a suprarenal of the same or of another animal was introduced into an opening in the lower pole of the kidney cortex, patterned as nearly as possible after the graft. The graft was held in place by sutures which brought together the cut edges of the kidney. Blood-clot between the surfaces of the graft and the kidney was prevented as far as possible.

Grafts developed in three rabbits so that suprarenal insufficiency failed to appear when the remaining suprarenal tissue was removed. Two were autotransplants while one was a heterotransplant. That these grafts functioned was shown by the symptoms of suprarenal insufficiency and death following their removal. Medullary tissue was evident histologically and chemically (reaction to chromate).

There was evidence of medullary function in two other cases although on account of the presence of accessory suprarenals, removal of the grafts did not produce death in spite of the fact that the other suprarenal had been removed.

The guinea pig is very unusual in its behavior to grafts. Elliott and Tuckett found that subcutaneous transplants from the bullock, sheep, rabbit, rat, hedgehog, fowl and another guinea pig caused edema. This was not due to epinephrin because suprarenals of the cat and dog failed to produce the effect. On the other hand, although guinea pig suprarenals were irritating for other guinea pigs, they produced no inflammation in the rabbit, cat or rat. This peculiar susceptibility of the guinea pig is unaccounted for. The available evidence indicates that suprarenal substitution by means of grafts is possible but difficult.

Reaction of the Suprarenals to Various Factors

Response to Toxins.—The suprarenals respond to many infections in such a way that it has been suggested that they exercise an important part as a detoxicating mechanism. An extensive consideration of the evidence would lead us too far into the domain of pathology; we propose merely to touch upon the problem.

It is known that many intoxications if prolonged induce hypertrophy of the suprarenals and especially of the cortex. Frequently in these cases the epinephrin content is lower than normal. Porak(*a*) has studied the effect of infection with rabies, tetanus, poliomyelitis, diphtheria and pneu-

monia. He found that the cortex was often hypertrophied and the epinephrin reduced, especially in long continued cases.

Dietrich has found typical changes in the cortex of individuals dying of peritonitis, sepsis and gas-gangrene. There were inflammation, degeneration, vacuolization and an increase in the number of lipoid vesicles.

Diphtheria is said to be particularly specific in producing vacuolization and hemorrhage of the suprarenals (Thomas). It is also claimed to reduce the epinephrin output (Luksch(*a*)).

The simpler organic and inorganic poisons may likewise destroy suprarenal tissue. Porak used strychnin, chloroform, lead and mercury. Graham was also able to produce necrosis, particularly of the cortex, by chloroform, dichlormethane or tetrachlormethane inhalations. Phenol has a similar although less effective action.

Repair is brought about by division of surviving cells in the whole cortex of the young individual but in the adult such regeneration is largely limited to the zona fasciculata. The chromaffin cells of the medulla also proliferate.

These conditions must be due to the action of the toxins reaching the gland through the blood stream. Whilst vacuolization might indicate an overactivity, hemorrhage and necrosis point merely to toxic action. The susceptibility of the suprarenals to toxins does not necessarily indicate that they are detoxifying organs.

Fatigue Effects.—Excessive muscular fatigue leads to vacuolization of the suprarenals (Bernard and Bigart, Bardier and Bonne) and to the disappearance of the lipoid-cholesterol bodies of the cortex (Laignel-Lavastine(*b*)). This indicates either an overactivity of the gland or else a reaction to the toxic products of fatigue, perhaps both. The value of epinephrin in postponing fatigue effects in skeletal muscle immediately suggests an overactivity of the gland. But proof is lacking. In the first place it has not been conclusively shown that the precursor of epinephrin is produced in the cortex. Nor are we sure that epinephrin is released at such a time in quantities sufficient to exhaust the cortex if that were the seat of formation. Such an interpretation therefore must be considered as merely suggestive.

Suprarenal Changes Following Severe Burns.—Although other organs are modified Weiskotten finds that the changes produced in the suprarenal are the most characteristic of any occurring in uncomplicated cases of superficial burns.

"The suprarenals are markedly swollen and deep red. The perisuprarenal fat tissue shows marked edema. On section, certain areas suggest extensive hemorrhage obliterating the normal markings."

"The gland cells are pale staining and much swollen. Many are apparently undergoing hydropic degeneration. Necrotic cells being in-

vaded by polymorphonuclear and endothelial leucocytes are not infrequent."

The changes are said to be comparable to those produced in the capsules by diphtheria toxin. Kolosko has described similar findings.

Response of the Suprarenal in Pregnancy.—During pregnancy both the suprarenal cortex and medulla hypertrophy, the former increasing much more than the latter (Guieysse(*a*), Stoerk and v. Haberer). This certainly indicates an overactivity on the part of these glands. Gabastou has found fat vacuoles constantly present in the suprarenal medulla throughout pregnancy. This may also indicate excessive activity.

Reaction to Cold.—It is interesting to note the observation of Cramer(*b*) that mice which resist exposure to cold possess suprarenals charged well with epinephrin while the suprarenals of those that die from exposure to cold are depleted of epinephrin. It has been shown that epinephrin injections increase heat production; therefore it is possible that epinephrin is necessary to meet such an emergency.

Effect of Cholesterol Feeding.—Because of the suggestion from some quarters that the suprarenal might be the seat of manufacture of the lipoids of the body it is interesting to observe the effect of cholesterol feeding on these glands.

Bailey has found enlargement of the suprarenals in rabbits and guinea pigs which were fed cholesterol daily. This appeared to be due to a storage of anisotropic globules. Such accumulation occurred also in the liver and medulla of the kidney.

Influence of Diet on the Suprarenals.—A scorbutic diet produces congestion and enlargement of the suprarenals so that animals dying of such fare possess glands double the normal weight. These changes were studied by McCarrison(*b*) in the guinea pig; they were brought about by feeding crushed oats and autoclaved milk. The abnormal conditions seen histologically were hemorrhagic infiltration and disintegration of both cortical and medullary cells. These modifications have been considered as prescorbutic, since they have been found in animals exhibiting no clinical evidences of scurvy during life. The epinephrin content of such glands was less than one-half of that in normal glands (estimation by Folin, Cannon and Denis' method).

McCarrison previously found that pigeons, in which polyneuritis was caused by feeding polished rice, developed enlarged suprarenals which contained more epinephrin than normal. He found that by the addition of accessory factors of "A" class in the form of fresh butter the epinephrin content fails to increase. He concludes that lack of "A" class substances caused the increased epinephrin in the polyneuritic pigeons.

Effect of Inanition on the Suprarenals.—The effect of inanition has been carefully worked out by Jackson(*c*)(*b*)(*m*) (see Stewart(*a*)(*c*)(*d*) for confirmation of Jackson's results) in the rat. He has found a variable

amount of cellular atrophy, especially in the middle cortical zone, and increased degeneration in the inner zone. The medulla is affected less. Mitosis in the young ceases but begins anew with refeeding. In adults the liposomes resist inanition to a considerable extent. The chromaffin action although weak in young animals can be diminished by underfeeding. On the other hand this reaction in the adult does not seem to be modified by inanition. This, you will notice, disagrees with the findings of McCarrison.

Pelligrini has noted that although there is diminution of the capsular chromaphil bodies in fasting, in the early stages this is accompanied by hyperfunctioning and in the later stages by a reduction in the function as well as regression in the medulla.

Byrne has described enlargement of the suprarenals in case of eight human subjects who had died of starvation. The increase was to about one and one-half natural size and appeared to be mostly in the cortex.

Physiology of the Suprarenal Cortex

About all we know concerning the function of the suprarenal cortex is that it is essential to life. Biedl's experiments upon extirpation of the interrenal bodies of fish have demonstrated this. Moreover, if we are to judge from the results of such an operation, the cortex would appear to be more vital than the medulla. The symptoms produced are similar to those resulting from complete suprarenal ablation in mammals. The relatively greater importance of the cortex has also been demonstrated by the works of Wheeler and Vincent in which they removed one suprarenal and half of the other, finally destroying the medulla of the remainder by cautery. When such animals succumbed the result could be attributed to cortical injury. Many of the animals survived the operation.

It is true that there are certain exceptional cases in which the cortex of both glands can be spared. But this is accounted for by the presence of accessory cortical bodies.

The importance of the cortical tissue is also indicated by the hypertrophy of such accessory tissue or of fragments of the suprarenal cortex in cases of experimental suprarenal insufficiency of long survival. In hypertrophy of the intact glands the increase is largely due to cortical growth, which confirms further the importance of this tissue.

The close anatomical relationship between the mammalian cortex and medulla has suggested to some the possibility of certain products being furnished by the cortex to be further elaborated in the medulla. Or epinephrin might actually be produced in the cortex and stored in the medulla (Abelous, Soulié and Toujan).

Toujan concluded from his study that epinephrin is produced in the

cortex. He incubated whole suprarenal tissue at 41° C. in the presence of $CHCl_3$ for twenty-four hours. There was an increase in the substances which give the iodin test. It was assumed that this represented an increase in epinephrin. He next chose two equal quantities of cortical and two of medullary tissue. One each of cortical and medullary tissue were at 0° C. and the other lot at 41° C. for twenty-four hours with the following results at the end.

Cortex	0°C.	0.77	mgm.	"epinephrin"	per	gm.	of	tissue
	41°C.	1.04	"	"	"	"	"	"
Medulla	0°C.	3.40	"	"	"	"	"	"
	41°C.	3.30	"	"	"	"	"	"

Bayer(*a*) claims that these results were due to protein decomposition.

More recently Voegtlin and Macht have obtained a pressor substance other than epinephrin from the cortex of the suprarenal. This substance was obtained by chloroform extraction of the cortical tissue desiccated by dehydrated sodium phosphate. After evaporation of the chloroform, the residue was extracted with CH_3OH. Repeated recrystallization gave white plates with a fatty luster the melting point of which was 50° C. The substance was sparingly soluble in water, and produced vasoconstriction in the blood vessels of frogs and rabbits. It was toxic when injected into mice. Its physiological properties were not changed by boiling with weak alkali.

A discussion of the cortical function must include the observations relative to growth and reproduction. The hypertrophy of the cortex during pregnancy indicates an increase in function, at present not understood. Verdozzi's(*a*) work has shown that the cortical hypertrophy of pregnancy is further increased if the mother is allowed to suckle her young. He suggests for this and other reasons (see relation to growth) that the suprarenal cortex is a factor in development and general nutrition.

Although Elliott and Tuckett failed to find a relationship between the cortex and the reproductive glands, others have been more successful in this respect. In some cases of precocious sexuality there is enlargement of the suprarenal, presumably the cortex is mostly responsible (Wooley(*b*), Bulloch and Sequeira(*a*)). Feeding suprarenal tissue to young animals stimulates the growth of the testis (Hoskins, R. G. and A. D.). On the other hand, according to Marassini(*b*), there is an increase in the cortex following castration.

Antitoxic power has been attributed to the cortex. The evidence is suggestive but far from conclusive. The lipoids are said to be able to neutralize toxins *in vitro*. Oleic acid, of which large quantities are contained in the cortex (Rosenheim and Tebb), can neutralize tetanus toxin. An emulsion of cortex detoxifies cobra venom (Myers).

The reaction of the cortex to bacterial toxins and other poisons

(see reaction of the suprarenal to various conditions) has been interpreted by some as due to hyperactivity rather than to a mere intoxication. Of course the toxic lesions might develop if the gland were unable to cope with the situation. However, these interpretations seem somewhat speculative in the present state of our knowledge.

The observations of Elliott and Tuckett seem to establish a relation between the skeletal musculature and the cortex. In the first place the lower a species is in the vertebrate scale the smaller is the proportion of cortical to chromaphil tissue at least in mammals. During the course of development of the individual, the cortex increases considerably while the medulla changes but slightly. In the guinea pig an increase in the weight of the body to five times is accompanied by a cortical increase of twelve times with little change in the medulla.

It is pointed out in connection with epinephrin effects on muscle, that the cortex becomes vacuolated after prolonged excessive muscular exertion. This may indicate hyperactivity due either to increased detoxication of the products of fatigue or to augmented secretory processes. If it could be shown that epinephrin precursors originate in the cortex, knowing the value of epinephrin in preventing the onset of fatigue, there would be cause to assume that such cortical vacuolation is the result of hypersecretion. There is some evidence of secretory activity on the part of the cortex. The doubly refracting substance increases during rest but decreases following muscular activity (Elliott and Tuckett).

All observations point to the importance of the suprarenal cortex. Throughout the vertebrate kingdom the cortex is the more constant of the two parts of the gland. It develops rapidly during the early growth of the individual and persists through old age. During conditions of stress it hypertrophies. Thus it enlarges during pregnancy and lactation, and perhaps also accompanying increased muscular development. It responds to toxins and infections in a manner not yet understood. These changes certainly indicate a valuable function.

Relation of Suprarenals to Growth

The suprarenals appear to bear a direct relationship to growth and reproduction, which is but a phase of growth.

In the first place it has been shown by R. G. and A. D. Hoskins that the suprarenal stimulates the growth of the gonads. They fed desiccated suprarenal to a series of forty-eight rats beginning at about the age of twenty days and lasting over a period of from two to eight weeks. These animals were fed daily as much dried suprarenal as could safely be given without causing digestive disturbances. It was found that no difference developed in the weight of the other ductless glands when compared to

the percentage weight of the corresponding gland in controls except in the case of the gonads. The ovaries and testes were larger in those animals fed suprarenal than they were in the controls. The observations on the testis were more conclusive because that series was larger.

This effect on the gonads must be largely due to the cortical portion of the suprarenal because very little of the epinephrin contained in the medulla is absorbed through the alimentary canal.

The amount of suprarenal tissue appears to be a factor in the determination of the number of offspring in a litter. Hoskins(*c*) has found that from a series of guinea pigs with one suprarenal removed, the number of offspring in the course of a year is notably below normal, although the animals appeared to be perfectly like their controls in development and behavior.

It is well known that the suprarenal hypertrophies in the mother during pregnancy. The mammalian method of gestation is probably responsible for this enlargement (Elliott and Tucket) because mere productive activity in itself does not appear to be responsible, for in the fowl, where the reproductive function is prolonged, there is no progressive development of the suprarenal glands. The placental circulation of the fetus may draw upon the maternal suprarenals for a cat near full term dies more speedily after excision of these glands than at other times (Elliott and Tuckett).

The work of Watrin(*b*), however, indicates that suprarenal hypertrophy during pregnancy is due to the presence of the placenta rather than to the fetus. At about the tenth day of gestation in the rabbit he removed the embryo through a small incision in the uterine wall. The wound healed and the placenta continued to develop. The hypertrophy of the suprarenals appeared to become as great as in normal gestation.

After birth if the young are permitted to take milk from the mother, the suprarenals of the latter continue to increase up to a certain period. On the other hand Verdozzi(*a*) has found that if, following birth, the guinea pig was hindered from suckling its young, the weight of the suprarenals, which at the moment of birth was generally higher than the normal weight, diminished rapidly and descended below the average normal figure. If the mother was permitted to suckle her young, the weight of the suprarenals increased rapidly, attaining the maximum at the end of about fifteen days. In the latter case the cortex hypertrophied, especially the fasciculated and reticulated zones, the lipoid and pigment increasing.

During the development of the individual there is an increase in the size of the suprarenals particularly the cortex, out of proportion to the increase in body weight (Elliott and Tuckett).

These observations lead us to believe that the suprarenals bear an important relation to growth and development.

The Significance of the Suprarenal Glands in Relation to the Vital Processes . . . . . *G. N. Stewart*

Control of the Epinephrin Discharge by the Nervous System—Action of Drugs upon the Epinephrin Output—Functions of Epinephrin in the Body—Epinephrin and Blood Sugar Content—The Epinephrin Store of the Suprarenals.

The Significance of the Suprarenal Glands in Relation to the Vital Processes

G. N. STEWART

CLEVELAND

The fundamental discovery by Oliver and Schäfer(*b*), in 1894, that extracts of the adrenal medulla cause on injection into the circulation marked pressor and other effects, was soon confirmed by Cybulski and Szymonovicz. A further important step was taken by Cybulski in showing for the first time that the active substance could be demonstrated in the blood of the adrenal veins. This he did by injecting the blood into a vein of another animal and observing that the same effects were produced as when an extract of the glands was injected—namely, a rise of pressure, slowing of the pulse and a slight increase in the rate of respiration. The extravagant claim that these quite rough qualitative experiments indicated that the nervous system which "up till now we were accustomed to regard as the highest authority in the organism must in a manner be deposed in favor of a new factor, without which even the activity of the nervous system would be impossible," hindered the acceptance of Cybulski's work.

Strehl and Weiss attempted to show that the pressor substance is given off to the blood by observing the changes in blood-pressure when a suprarenal vein is temporarily occluded by a ligature and then released. They obtained a marked fall of pressure on occluding the vein and a rise on releasing it. But this occurred only in a minority of their experiments, and according to Asher, their result was due to errors of technique. It could not be confirmed by Kahn(*a*) and Young and Lehman saw a distinct increase of blood-pressure in only 3 out of 8 experiments on dogs on releasing the suprarenal veins, while occlusion of the veins caused no noticeable effect.[1]

[1] (Throughout this work controversial points have for the most part received only brief consideration, pending the accumulation of conclusive data. As regards the control of suprarenal secretion, however, the problem is of such fundamental importance and the views of the most competent investigators are so widely divergent that it has seemed wise to present the matter in this and the succeeding chapter from two distinctive points of view. This procedure serves to bring out numerous important data as well as to illustrate the difficulties inherent in investigations in the field of the internal secretions.—R. G. H.)

Hoskins and McClure(*a*) saw no immediate fall in blood pressure after ligating off the adrenal glands in dogs. The experiments of Dreyer, Tscheboksaroff,(*a*) Joseph and Meltzer, Asher and Elliott(*c*) proved conclusively that stimulation of the splanchnic nerve causes epinephrin to pass from the corresponding suprarenal into the blood. The work of these investigators will be alluded to again in discussing the nervous mechanism controlling the epinephrin secretion. Although not directly concerned with the question, whether the glands are constantly giving off epinephrin, still less with the question of the magnitude of the output, the demonstration

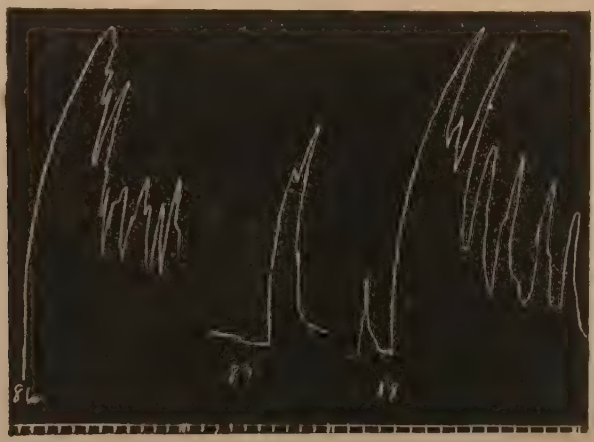

Fig. 1. Uterus tracings. At 86, Ringer's solution was replaced by serum from dog's suprarenal vein blood; at 87 by sediment from the blood (mainly corpuscles); at 88, by the defibrinated blood. All the blood specimens were diluted with 14 volumes of Ringer's solution before application to the segment. The tone-increasing action of the serum was much greater than that of the sediment, the blood being intermediate. Intestine tracings showed that the specimens occupied the same relative position as regards the amount of inhibition, the sediment causing a very slight effect. Time marked in half minutes, as in all the figures unless otherwise stated. (Reduced to one-half.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

that the suprarenal medulla is under the control of secretory nerves increased the probability that a physiological output occurs. Tscheboksaroff remarked indeed that the reaction on which he as well as Dreyer relied (the rise of pressure produced by injecting intravenously into a dog a given quantity of suprarenal vein blood from another dog) was much diminished by division of the splanchnic, indicating that some epinephrin was being given off with intact splanchnic nerves in the absence of artificial stimulation.

Trendelenburg(*a*)(*b*) using the frog perfusion method (Laewen preparation) found concentrations of epinephrin in the suprarenal vein blood of cats varying from 1:360,000 to 1:1,000,000. O'Connor(*a*)(*b*), also working with the frog perfusion method, showed that in the rabbit, after section of the splanchnics, the epinephrin secretion of the suprarenals is

greatly diminished or abolished. He was always able to demonstrate epinephrin in the plasma of blood from the suprarenal veins of rabbits in the concentration of 1:1,000,000 to 1:5,000,000. Since, as demonstrated by Stewart and Rogoff(*d*)(1917), the epinephrin is practically confined to the plasma the concentration in the blood would be about half as great (Fig. 1). Ehrmann's(*a*)(*b*) observations on rabbits, although constituting the first attempt to measure the output of epinephrin, were seriously handicapped by the fact that he employed the frog's eye method for estimating

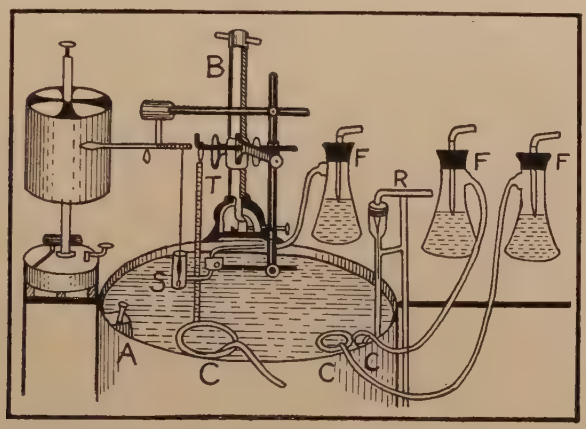

Fig. 2. Arrangement for estimating concentration of epinephrin in suprarenal vein blood, showing small cylinder in which the rabbit intestine (or uterus) segment is suspended, with side tube for supplying oxygen. Vessels for the stock of intestine (and uterus) and for warming the Ringer's solution and the blood samples are immersed in the large constant temperature bath. *A*, holder of copper gauze for heating blood specimens to temperature of the large bath; *B*, stand supporting recording arrangement and small cylinder *S* (with side tube for oxygen) containing intestine (or uterus) segment; *C*, cylinders containing Ringer's solution for washing and stock of rabbit's intestine and uterus; *F*, flasks through which oxygen is passed to the cylinders, the oxygen being forced through the flasks from the bottles, *B*, shown in Fig. 3; *R*, temperature regulator; *T*, thermometer.

the epinephrin concentration in the suprarenal vein blood. It is not suitable for this purpose nor is it delicate enough. He obtained concentrations of 1:1,000,000 to 1:10,000,000, while Waterman and Smit with the same method obtained smaller concentrations. Borberg(*a*), on the other hand, got much higher concentrations than Ehrmann (1:250,000 to 1:1,000,000) in 3 rabbits after piqûre. In none of these observations was sufficient attention paid to the measurement of the rate of blood flow from the suprarenals. Without this the output cannot be calculated.

Hoskins and McClure(*b*) in 5 dogs found the concentration in the suprarenal vein blood to correspond to from 1:2,000,000 to 1:8,000,000 of a solution of "adrenalin hydrochlorid" (probably something like 1:3,000,000 to 1:10,000,000 of the base). They employed what is probably the most accurate method for assaying epinephrin in bloood, the rabbit in-

testine segment method introduced independently by Stewart(*a*) (1911) (Figs. 2 and 3) and by Hoskins(*d*) (1911-12). Stewart(*a*) emphasized the importance in cases in which there is a possibility that the inhibition of the intestine might be caused by something else than epinephrin of checking the intestine reaction by a reaction such as that given by the rabbit's uterus, preferably the virgin or at least the non-pregnant uterus, in which

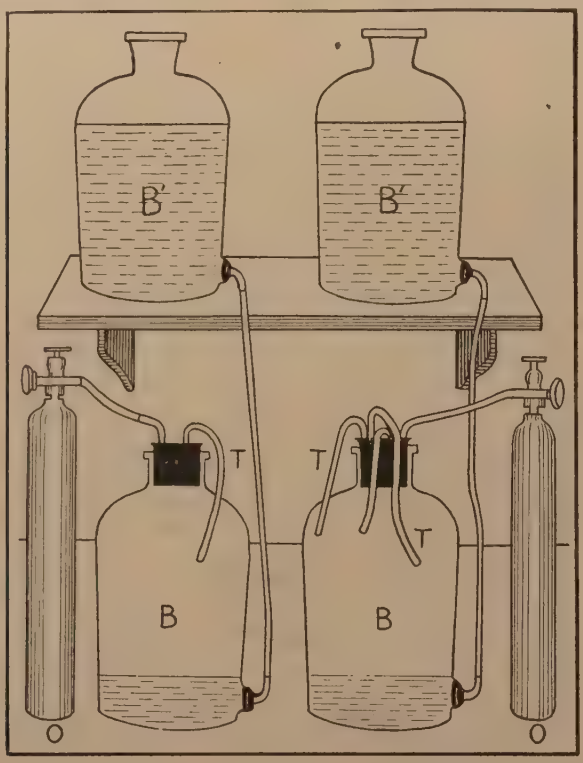

Fig. 3. *B*, bottles filled with oxygen from the oxygen cylinders *O*. The oxygen passes out of the bottles as water enters them from the bottles *B'*, and is conveyed by the tubes, *T*, to the flasks *F* shown in Fig. 2.

the tone is increased by epinephrin. For instance, occasionally, as reported by Cannon and Hoskins, the blood of the right heart or the general blood in asphyxia may contain a substance which causes the characteristic inhibition of the intestine. In such a case it has been shown by Stewart that the blood inhibits the uterus preparation also, and the reaction is not due to epinephrin. Although this may be occasionally seen, Cannon and de la Paz are unqestionably correct in stating that, practically, epinephrin is the only substance in blood which causes well marked inhibition of the intestine preparation. This, however, is with the proviso that the tests are carried out under definite and constant conditions with regard to oxygen supply, temperature, exposure of the preparation, etc. In

elaborating the method further for quantitative purposes Stewart(*b*) (1912) and Stewart and Zucker(*a*, *b*) (1913) made it clear that no advantage was to be gained from employing unclotted blood or plasma for the tests on such objects as intestine or uterus instead of defibrinated blood or serum, as claimed by O'Connor(*a*) although they entirely confirmed his finding, that for vascular test objects (frog perfusion preparation or artery rings) it is essential to prevent clotting, on account of the vasoconstrictor

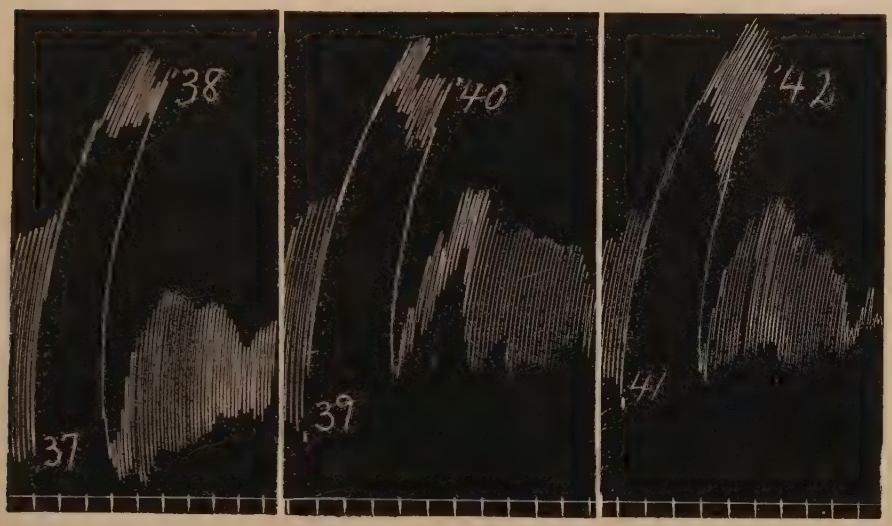

Fig. 4. Intestine tracings forming a small sample of those used in the epinephrin assay of a suprarenal blood specimen from a cat. At 37 and 39, Ringer's solution was replaced by indifferent (jugular) blood diluted with an equal volume of Ringer's solution. At 38 and 40 this was replaced by jugular blood made up with "adrenalin" to a concentration of 1:2,000,000 and 1:3,400,000 respectively, the "adrenalin" blood being diluted with an equal volume of Ringer's solution before application to the segment. At 41, Ringer's solution was replaced by jugular blood, and this at 42 by a suprarenal blood specimen, both specimens being diluted with an equal volume of Ringer's solution. The inhibition produced by 1:2,000,000 "adrenalin" is obviously much greater than that produced by the suprarenal blood, which was assayed at 1:3,400,000. (Reduced to two-thirds.) (After Stewart and Rogoff, *Am. J. Physiol.*)

substance set free from the platelets, as shown by Zucker and Stewart and later by Janeway, Richardson and Park, who like H. A. Stewart and Harvey(*a*) used and developed the artery ring method of Meyer.

The quantitative relations of the epinephrin output of the suprarenals under definite experimental conditions were next investigated by Stewart and Rogoff. In a series of papers they showed(*b*)(1916) that in all the groups of animals studied (cat, dog, rabbit, and monkey), and in every individual, a demonstrable amount of epinephrin is invariably present in the blood of the suprarenal veins. If it occasionally seems to be absent, this is simply because the test object is not sufficiently sensitive, as shown by obtaining a positive result with a more sensitive object. They relied mainly upon assays of the epinephrin concentration made in the drawn

blood upon rabbit intestine (and uterus) segments (Fig. 4), but corroborated their results by two other methods which are spoken of as methods of auto-assay, because the blood is not withdrawn, but its content of epinephrin is estimated by reactions elicited in the animal itself. In one of these methods blood from the suprarenals is allowed to collect in a pocket of the inferior vena cava for a definite time, and is then released while a blood-pressure tracing is being taken. A rise of pressure is obtained, the amount of which is then imitated by the injection of known amounts of epinephrin (Fig. 5). In the other method of auto-assay the dilatation of the pupil (in cats) of an eye, sensitized for epinephrin by previous removal of the superior cervical ganglion, is observed when the suprarenal blood, collected in the cava pocket, is released, and the reaction imitated by injection of epinephrin. The "adrenalin" solution of Parke, Davis & Co. is assayed by the colorimetric method of Folin, Cannon and Denis and the epinephrin given off by the adrenals is always expressed in terms of the base.

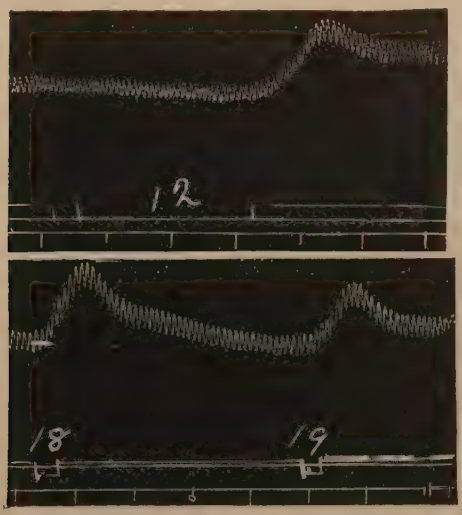

Fig. 5. A sample of blood pressure tracings used in an auto-assay of the epinephrin liberated during splanchnic stimulation in a cat. The right splanchnic was stimulated in the abdomen after section of both splanchnics. The blood from the suprarenals was collected in a cava pocket, which was then released. Stimulation began at the point indicated on the signal line a short time after closing of the pocket. Good rise of pressure after opening the pocket at 12, due to epinephrin; 18 and 19, "adrenalin" injections to assay the amount of epinephrin liberated; 18, 0.3 c.c. of "adrenalin" (1:150,000); 19, 0.2 c.c. of the same solution. (Reduced to two-thirds.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

The average output for 29 cats (under urethane), the lumboadrenal vein blood of which was assayed on rabbit intestine segments, was 0.00025 mgm. of epinephrin per kgm. of bodyweight per minute, and for 16 etherized cats 0.0002 mgm. per kgm. per minute. The range in the different animals was from 0.00015 to 0.00045 mgm. per kgm. per minute in the urethanized animals and from 0.0001 to 0.0005 mgm. per kgm. per minute in the etherized cats (*e*, s) (1917) (1919). The usual range is far narrower than is indicated by these extreme limits. For the great majority of the results lie quite close to the mean. Thus for 25 out of the 29 urethanized cats the first significant figure in the output is either 2 or 3. The concentration of epinephrin in the suprarenal blood in the urethanized cats ranged from 1:800,000 to 1:14,000,000 and in the etherized animals from 1:1,-

300,000 to 1:9,000,000. The limits of concentration have not the same significance as the limits of output. For it has been shown(*f*)(1917) that in one and the same animal during an experiment the concentration varies inversely as the rate of blood flow through the suprarenals within the limits of error of the method of assay employed. In other words, while the output remains constant the concentration of epinephrin in the suprarenal vein blood may undergo great variations. Another way of stating the same thing is that under our experimental conditions the epinephrin is given off by the suprarenals at a steady rate, which is independent of changes in the blood flow, just as carbon dioxid is given off by resting muscles at a steady rate, which is not influenced by variations in the rate of blood flow. Trendelenburg's(*b*) statement (1911), that when the blood-pressure (in cats) is reduced by hemorrhage and the minute outflow of blood from the suprarenals correspondingly diminished the epinephrin concentration increases so much as to compensate for the decreased flow, is in agreement with the results of Stewart and Rogoff, although the number of his observations was small and some of them were made by a method which seems open to serious error, the estimation of the epinephrin concentration by the rise of pressure produced by injection of a given quantity of cat's serum into guinea pigs. His rough estimate of the output of epinephrin at something like 0.0003 mgm. per minute per animal is also of the same order of magnitude, although no doubt smaller if meant as an average. Ehrmann's statement(*b*)(1905) that the amount of epinephrin given off in the cat is much less than in the rabbit is quite inaccurate. In so far as it is not based upon technical errors it means only that the concentration was greater in the rabbit, which is likely enough as the blood-pressure was probably lower and the blood flow, therefore, smaller. This writer habitually confuses concentration with rate of output. O'Connor's incidental statement, in an otherwise excellent paper, that in the rabbit the output seems to diminish as the blood flow diminishes is probably erroneous, unless, indeed, it applies to a condition of shock, more easily induced in the rabbit than in the dog or cat, so profound and so prolonged that the central nervous mechanism on which the secretion depends has suffered materially. His estimate of the output at 0.0007 to 0.00014 mgm. per minute per rabbit agrees sufficiently with the results of Trendelenburg on the same animal (0.00015 to 0.0002 mgm. per kgm. per minute) and with the few observations made on the rabbit by Stewart and Rogoff.

In 17 dogs anesthetized with morphin and ether or with ether alone, the concentrations of epinephrin in the suprarenal vein blood, assayed on rabbit's intestine segments, were found to vary between 1:1,800,000 and 1:18,000,000. The average output per kgm. of bodyweight per minute was 0.00022 mgm. (Stewart and Rogoff(*e*))(1917). Assuming that the "adrenalin" solution employed by Hoskins and McClure(*b*) contained 70 per cent of base, their average for 5 dogs estimated by the same method

would be about 0.00018 mgm. Popielski's(*a*) result of 0.004 mgm, per kgm. per minute for the dog is probably 20 times too great. It is worthless because of the method employed (compression of the aorta for a given time and imitation of the rise of pressure produced on release by injection of "adrenalin"). He is perfectly correct, however, in stating that a demonstrable effect on the blood-pressure after release of the aorta can sometimes be obtained. This is due to the release of blood from the suprarenals containing epinephrin, secretion of which has been going on steadily during the period of occlusion.

In two macaque monkeys examined by Stewart and Rogoff(*e*)(1919) the output per kgm. per minute was respectively 0.0002 mgm. and 0.00015 mgm.

It is obvious that a surprisingly close agreement exists in the results of those observers who have estimated the epinephrin output in drawn suprarenal vein blood on suitable test objects by adequate methods. This is true not only of one group of animals, but of all the mammals carefully examined. The presumption is strong that the output observed is not an artificial phenomenon varying widely with the anesthetic, the operation and the kind of animal, as an artificially excited discharge might be expected to do. This presumption is further strengthened by the fact that when the rate of blood flow is altered within very wide limits it is the concentration which varies and not the amount of epinephrin given off per unit of time.

Control of the Epinephrin Discharge by the Nervous System

The fact just noted would of itself be sufficient to dispose of the contention of Popielski(*b*) that the increased output caused by stimulation of the splanchnic nerve is not a true secretion but is simply due to the washing out of more epinephrin when the blood flow through the gland is increased by the excitation of the vasodilator fibers discovered by Biedl (*a*)(1897) in the splanchnic and by the rise of pressure. His arguments against the true secretory function of the splanchnics for the suprarenal glands are entirely devoid of value. That pressure on or manipulation of the glands liberates epinephrin is true enough, as was shown by Stewart and by Stewart, Rogoff and Gibson (1916) (Fig. 6), but it is quite erroneous to say that it does not pass into the circulation until the gland is flushed out with blood, as after stimulation of the splanchnic. He estimated, by testing (on rabbit intestine segments and by injection into rabbits) blood withdrawn from the inferior vena cava by a catheter during pressure upon the suprarenal, that the blood of a 13 kgm. dog would contain 2 mgm. of epinephrin. This would represent

at least the entire store of a pair of well stocked suprarenals and would correspond to a concentration of 1:500,000 for the whole volume of blood, an impossible result.

That stimulation of the peripheral end of the splanchnic nerve causes an increased output of epinephrin into the blood leaving the suprarenals, was shown by Dreyer, whose work was confirmed and extended by Tscheboksaroff(*a*) by the same method, observation of the rise of pressure produced in a dog by injection of suprarenal vein blood from another dog,

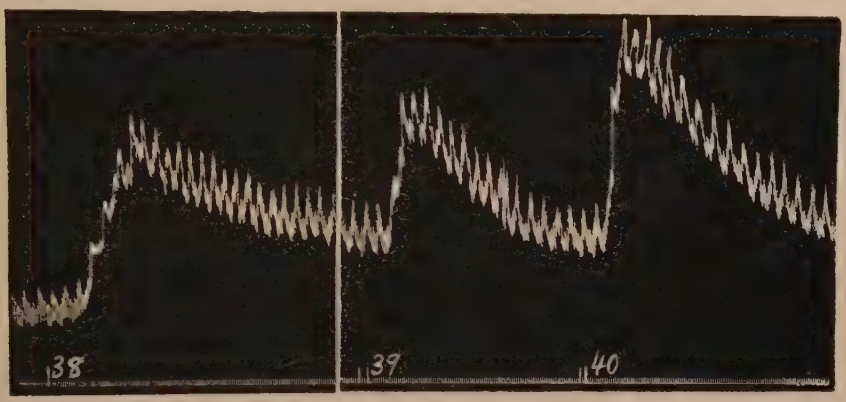

Fig. 6. Blood pressure tracing from a dog weighing 10 kgm. to show effect of massage of the suprarenals in liberating epinephrin. At 38, a cava pocket which had been closed for 6 minutes was released. For 5 minutes during closure of the pocket gentle massage had been practised at intervals. On release, the blood pressure rose from 32 to 100 mm. of mercury and fell only slowly. Just before the massage the release of a pocket kept closed for an equal time was followed by only a slight increase of pressure. (The spinal cord had been cut and various experiments made on the animal for 2 hours before the massage.) At 39, 0.5 c.c. of "adrenalin" (1:13,300) was injected and raised the blood pressure from 65 to 110 mm. of mercury. At 40, injection of 1 c.c. of "adrenalin" (1:13,300) caused an increase of pressure from 65 to 140 mm. of mercury. The amount of epinephrin discharged by the 5 minutes massage was approximately estimated at not less than 0.04 mgm. Time trace, seconds. (Reduced to two-thirds.)

obtained with and without splanchnic stimulation. This is a good method, although not as sensitive as the intestine segment method, and can also be used for quantitative estimation of the amount of epinephrin liberated. Asher confirmed these results in another way, by demonstrating that in rabbits from which all the abdominal and pelvic viscera except the suprarenals had been removed, stimulation of the splanchnic caused a rise of blood-pressure, which did not occur if the suprarenal veins were clipped off. Evidence of a different nature was supplied by Joseph and Meltzer (1911-12), and soon thereafter in much greater detail by Elliott(*c*) (1912). They showed that when the peripheral end of a splanchnic nerve is stimulated (in the cat) the pupil of an eye, sensitized for epinephrin by previous removal of the superior cervical ganglion, is dilated after such a latent period as would be required for epinephrin to reach the eye in

the circulation from the suprarenal gland. The nictitating membrane may also be retracted. When the experiment is repeated after removal or ligation of the suprarenal, there is either no dilatation of the pupil or a very slight one. It was demonstrated by Stewart, Rogoff and Gibson that the latent period of the liberation of epinephrin from the glands on stimulation of the splanchnics is so short that the time interval after which the eye response occurs is sensibly the same, whether it is evoked by splanchnic stimulation or by the injection at the level of the suprarenals of a quantity of "adrenalin" sufficient to elicit a response similar in character and amount. The minimum period of stimulation of the splanchnic needed to liberate sufficient epinephrin to elicit a response in the denervated eye is very brief (a fraction of a second). Anything which interferes with the passage of the blood from the suprarenals to the eye during stimulation of the splanchnic, *e.g.,* clipping of the inferior cava, hinders the response, which, however, is obtained when, after stopping stimulation, the obstruction to the passage of the blood is removed. The demonstration is complete that the eye reactions are due to augmented epinephrin liberation under the influence of stimulation of the splanchnic.

That the spontaneous output is entirely under the control of nerves is well established. The best proof is furnished by the quantitative estimation of the output before and after section of the splanchnics and other efferent paths carrying the secretory fibers. It has been shown (Stewart and Rogoff(*e*) 1917, 1919) that the output may be reduced (in the cat and dog) so much that no epinephrin could be detected in the suprarenal vein blood even when segments sensitive enough to detect 1/1,000 of the normal output were employed. In a macaque monkey no epinephrin could be detected, although the segment gave a distinct reaction with 1:330,000,000 "adrenalin," and the output could not have been 1/100 of the normal.

Although the bulk of the efferent epinephrin secretory fibers run in the major and minor splanchnic nerves, there is evidence that some of the fibers may pass from the abdominal sympathetic chain to the glands. For after section of the splanchnics a detectable, though much reduced, output of epinephrin may be observed (in the cat and dog). There is probably some variation in different individuals in this regard. Further, it has been shown by Elliott(*e*) (1912) (in cats) that the store of epinephrin in the suprarenal is only fully protected against depletion under the influence of anesthesia and other conditions, if all the fibers coming to the semilunar ganglion are cut. And, as will be pointed out later, the most satisfactory hypothesis of the depletion produced by some drugs at least, such as ether, is that the formation or the storage of epinephrin in the suprarenals is interfered with while the spontaneous discharge, which is strictly under the control of the nervous system, goes on steadily in the case of the gland the nerves of which are intact, but

not in the denervated gland, so that at the end of some hours a marked deficiency in the store of the former is established.

In the dog and cat there seems to be no crossing of epinephrin secretory fibers from one splanchnic to the opposite suprarenal. It has been stated by Kahn(*b*) and by Nishi(*b*) that in the rabbit the right suprarenal seems to derive from the left splanchnic a portion of the nerve supply concerned in changes in the epinephrin store and in the liberation of epinephrin. The much greater difficulty experienced by Stewart and Rogoff(*c*) in producing a marked differential effect on the epinephrin store

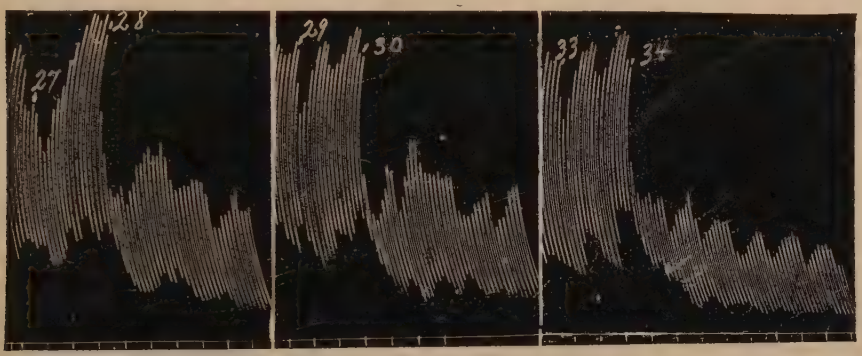

Fig. 7. Intestine tracings constituting a small sample of those used in the assay of suprarenal blood specimens from a cat before and after transection of the cord above the origins of the 6th pair of cervical nerves. At 27, 29 and 33 Ringer's solution was replaced by indifferent (venous) blood and this at 28 by indifferent blood to which was added "adrenalin" to make a concentration of 1:660,000; at 30 by a suprarenal blood specimen collected 5½ minutes after section of the cord; at 34 by indifferent blood to which was added "adrenalin" to make a concentration of 1:530,000. All the blood specimens were diluted with 3 volumes Ringer's solution (the "adrenalin" bloods after adding the "adrenalin"). The suprarenal blood was assayed at 1:700,000, corresponding to an output of 0.00021 mgm. epinephrin per kgm. per minute, precisely the same as that given by a suprarenal specimen collected before cord section, although the concentration of the latter specimen was of course much less (1:6,000,000), corresponding to the much greater blood flow associated with the higher pressure. (Reduced to three-sevenths.) (After Stewart and Rogoff, *Am. J. Physiol.*)

of the two suprarenals in these animals, after section of the splanchnics on one side, tends to confirm this suggestion.

With regard to the position of the central nervous mechanism controlling the epinephrin secretion, the best established fact is that, after section of the cervical cord in acute experiments in the cat the output may not be at all diminished (Stewart and Rogoff 1917, 1920 (*i, v*)) Fig. 7. This result is the rule after bloodless elimination of the upper parts of the central nervous system, by ligation (in cats) of both carotids and vertebrals, or of the innominate, left subclavian proximal to the origin of the vertebral, and other arteries supplying the head (Stewart, Guthrie, Burns and Pike, Fig. 8). In dogs and monkeys the output was diminished in acute experiments by cervical cord section owing, it is suggested, to spinal shock of an epinephrin-secreting center in the upper part of the

thoracic cord, although usually the output was still substantial. The result is not modified essentially by varying the level of the cervical section. Even after section as low as the last cervical segment, epinephrin continues to be liberated, and this liberation has all the characters of the normal secretion, and is sustained through the same nerve paths connecting the cord with the suprarenals. In experiments in which the animals were allowed to survive the cervical cord section for some time (up to 13 days), the output never equalled the average ordinary output, although it was often substantial. Strychnin increases markedly the output, by a central

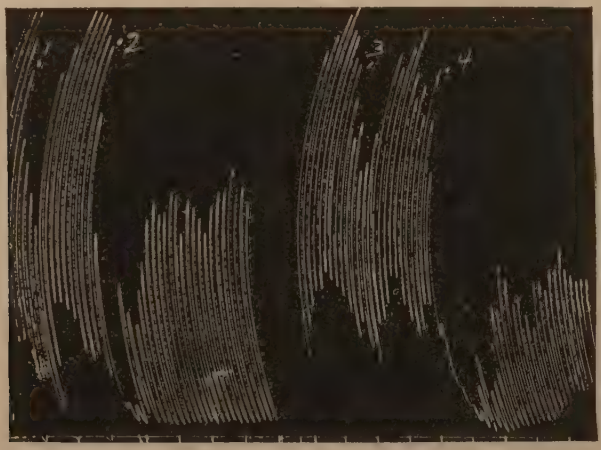

Fig. 8. Intestine tracings. At 1 and 3, Ringer's solution was replaced by indifferent (venous) blood and this at 2 by a suprarenal blood specimen collected in a cat before tying off the head arteries; at 4, by a suprarenal specimen collected after tying off these arteries. All the blood specimens were diluted with 3 volumes Ringer's solution. From numerous tracings (not reproduced) it was shown that the output of epinephrin was quite as great after the brain and bulb had been eliminated as before, the smaller blood flow per minute being fully compensated by the increased concentration of the epinephrin. (Reduced to one-half.) (After Stewart and Rogoff, *Am. J. Physiol.*)

action (on the thoracic cord), after transection of the cervical cord both in acute and survival experiments (Figs. 9 and 10). It is the uppermost thoracic segments which seem to be related to the epinephrin output, and by appropriate section of the dorsal cord lower down the output can be diminished or abolished within the limits of sensitiveness of the methods employed for its detection. There is no definite evidence as to the existence of centers situated higher up in the central nervous system, although from analogy we should expect that impulses coming from above might modify the activity of the spinal center. Theoretically, such impulses might augment or diminish the epinephrin output. It has sometimes been observed that the output after destruction of the cerebral cortex, or section of the brain stem above the corpora quadrigemina was increased decidedly beyond the normal range, suggesting that an inhibition had been removed. Elliott (*c*) (1912) considers that a center concerned in the depletion of the epi-

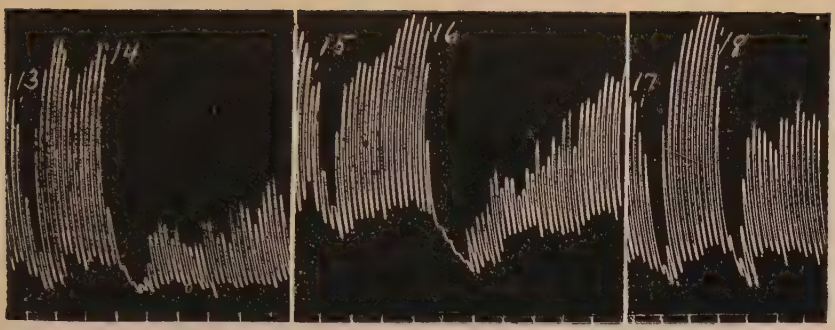

Fig. 9. Intestine tracings. Blood specimens from a cat in which the cord had been transected between the first and second dorsal segments 4 days previously. At 13, 15 and 17, Ringer's solution was replaced by indifferent (venous) blood, and this at 14 by indifferent blood to which was added "adrenalin" to make a concentration of 1:130,000,000; at 16 by a suprarenal blood specimen collected before injection of strychnin; at 18 by indifferent blood to which was added "adrenalin" to make a concentration of 1:195,000,000. All the blood specimens were diluted with 3 volumes Ringer's solution (the "adrenalin" bloods after adding the "adrenalin"). The concentration of epinephrin in the suprarenal blood was assayed at 1:150,000,000, corresponding to an output of only 0.0000025 mgm. per kgm. per minute, one-hundredth of the normal average. The segment was exceptionally sensitive. (Reduced to one-half.) (After Stewart and Rogoff, *Am. J. Physiol.*)

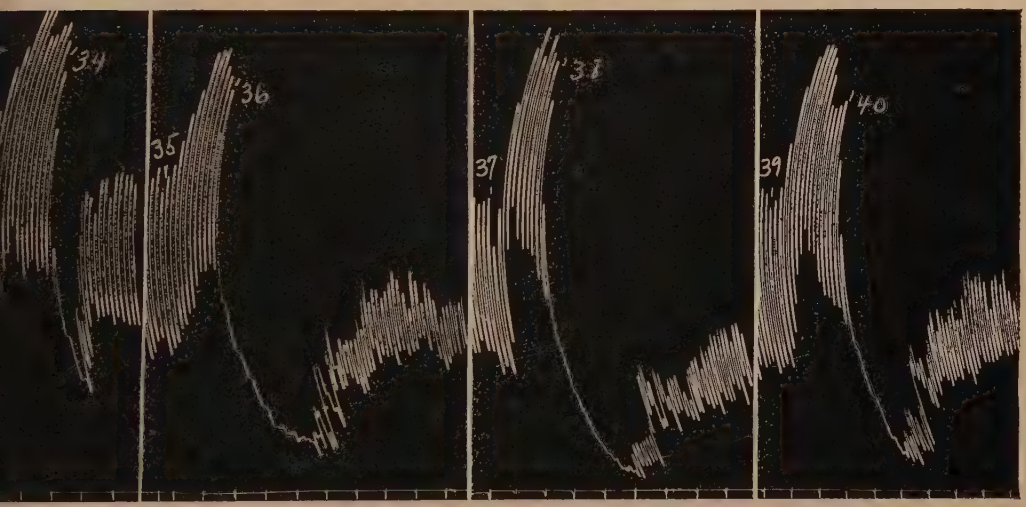

Fig. 10. Intestine tracings. Blood specimens from the same cat as Fig. 9. At 33, 35, 37, and 39, Ringer's solution was replaced by indifferent (arterial) blood, and this at 34 by indifferent blood to which was added "adrenalin" to make a concentration of 1:6,600,000; at 36 by a suprarenal blood specimen (collected 8 minutes after intravenous injection of strychnin) diluted with 3 volumes of indifferent blood; at 38, by indifferent blood to which was added "adrenalin" to make a concentration of 1:2,700,000; at 40, by the same suprarenal blood specimen diluted with 3 volumes of indifferent blood. All the blood specimens were diluted with 3 volumes Ringer's solution (the "adrenalin" bloods after adding the "adrenalin"). The suprarenal blood (after strychnin) was assayed at 1:1,000,000 epinephrin, corresponding to an output of 0.00025 mgm. per kgm. per minute, which is the normal average. Strychnin accordingly increased the output in this case 100 times. (Reduced to one-half.) (After Stewart and Rogoff, *Am. J. Physiol.*)

nephrin store under anesthesia, etc., is situated in the bulb close to the vasomotor centers, and that depletion does not occur when the cord is divided below this level, under the influence of conditions which would otherwise have caused it. But observations on the store cannot be directly transferred to the liberation of epinephrin from the suprarenals. One of the best illustrations of this is the fact that, as shown by Elliott, it is difficult to produce by stimulation of the splanchnic any detectable change in the store of epinephrin, while the liberation is markedly increased. The simplest explanation would seem to be that the splanchnic also contains fibers which increase the rate of formation of epinephrin in the gland, as suggested by Tscheboksaroff(*a*). It is not inconsistent with this that after section of the splanchnic, and indeed, as far as possible, of all the nerves going to the suprarenal, a depletion in the store is entirely made good in a day or two. The chromaphil cells may very well have the power of accumulating epinephrin in the absence of innervation up to a certain maximum, and if they are losing none, as after section of the nerves, a considerable deficiency may be made up in 24 or 48 hours. But under the rapid mobilization which occurs when the secretory nerves are stimulated, it might be expected that the replenishment of the store should also be accelerated. With very prolonged stimulation of the splanchnic (9 hours), with short periods of excitation alternating with longer rest periods so that each stimulation is effective, a distinct depletion was found after 300 stimulations by Stewart and Rogoff(*c*)(1916). They concluded that an amount of epinephrin approximately equal to the initial load (0.20 mgm.) must have been formed in the gland whose splanchnic was stimulated during the time the experiment lasted.

Concerning the possible afferent paths through which the epinephrin output can be affected, little or nothing is known. Richards and Wood(*b*), working with rabbits and testing the suprarenal vein blood collected from a cava pocket on cat's intestine strips, came to the conclusion that stimulation of the depressor caused diminution of the rate of liberation of epinephrin. Incidentally they observed that stimulation of sensory nerves (central end of the median) did not increase the output. Tscheboksaroff(*a*) from the increase of blood pressure produced in a dog by the injection of suprarenal vein blood from another dog convinced himself that "the increase of blood-pressure caused by stimulation of a sensory nerve (sciatic) has no effect upon the quantity of secreted adrenalin."

Cannon and Hoskins withdrew blood from the inferior cava by a fine catheter passed up through the femoral vein to above the level of the suprarenals (in cats), and tested the blood on rabbit's intestine segments. They concluded that stimulation of sensory nerves (central end of the sciatic) increased the output of epinephrin. Anrep(*a, b*) stated that if the nerves of a hind limb or a kidney (in the dog) be cut, these denervated parts respond to stimulation of afferent nerves (central end of sciatic)

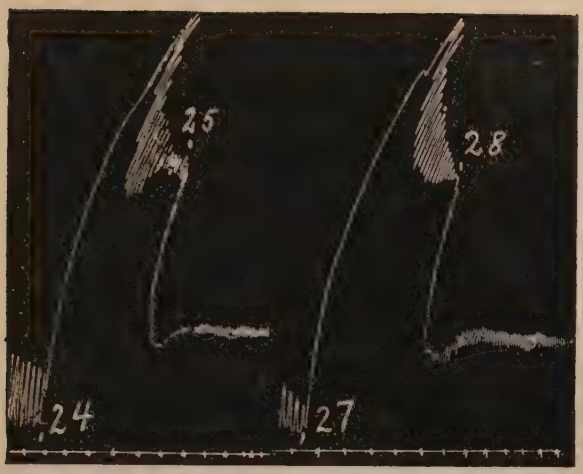

Fig. 11. Intestine tracings. At 24, Ringer's solution was replaced by indifferent (jugular) blood from a dog and this at 25 by a suprarenal blood specimen collected during sciatic stimulation. At 27, Ringer's solution was replaced by jugular blood and this at 28 by a suprarenal blood specimen collected without stimulation of nerves. (Reduced to two-thirds.) (After Stewart and Rogoff, *J. Exper. Med.*)

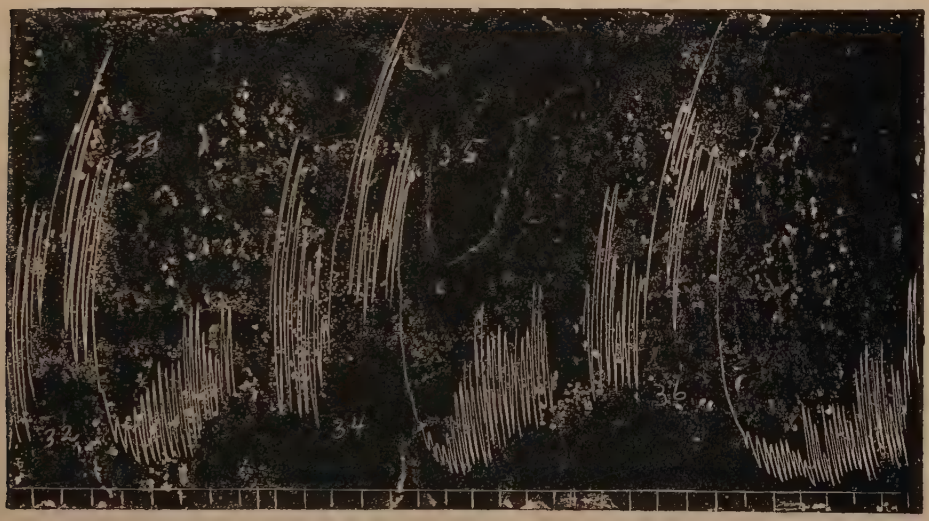

Fig. 12. Intestine tracings. At 32, Ringer's solution was replaced by indifferent (jugular) blood and this at 33 by a suprarenal blood specimen (the third) collected (in a cat) without asphyxia. At 34, Ringer's solution was replaced by jugular blood and this at 35 by a suprarenal blood specimen (the 4th) collected during asphyxia. At 36, Ringer's solution was replaced by jugular blood and this at 37 by another suprarenal blood specimen (the fifth) collected without asphyxia. All the blood specimens were diluted with 16 volumes Ringer's solution before application to the segment. The assay showed that the differences in the concentration of epinephrin in the various specimens were balanced by the differences in the rate of flow, so that no influence of asphyxia upon the rate of output of epinephrin could be demonstrated. (Reduced to two-thirds.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

by a vaso-constriction if the suprarenals have not been interfered with, but only show the initial passive dilatation due to the rise of blood-pressure, if the suprarenals have been extirpated. He drew the conclusion that stimulation of the sciatic reflexly increases the rate of liberation of epinephrin. But granting that the characteristic vaso-constriction can only be elicited with intact adrenals, and von Anrep's careful work has been recently confirmed by Pearlman and Vincent, this does not prove that during stimulation of the nerve more epinephrin is being poured into the blood per unit of time than without stimulation, for during the stimulation the condition of the test object is greatly altered. The rise of blood-pressure must necessarily increase the rate of blood flow through the denervated region. If the suprarenals merely continue to discharge epinephrin at the normal rate, the amount of epinephrin passing per unit of time through the vascular tract in question is abruptly and markedly augmented. If such denervated areas are as sensitive to epinephrin as is claimed, they may be expected to respond to this increase in the amount of epinephrin traversing them, even if no change whatever has taken place in the rate of liberation from the suprarenals. That such a redistribution of the epinephrin-containing blood, without any increase in the output, can elicit the reaction is shown by the observation of v. Anrep himself, that "if one splanchnic nerve is intact while the suprarenal on the other side is extirpated, stimulation of the splanchnic nerve on the side of the extirpated suprarenal may still cause constriction of a denervated limb. Only after the other splanchnic nerve is cut does the constriction disappear." The reaction studied by v. Anrep accordingly is not at all out of harmony with the observations of Stewart and Rogoff (*j*) (1916, 1920), who, working with cat's suprarenal blood obtained from a cava pocket, and estimating quantitatively the rate of epinephrin output on rabbit intestine segments (Fig. 11), failed to obtain any definite effect upon the output when sensory nerves were stimulated. They pointed out that observations, made without regard to changes in the rate of blood

Fig. 13. Uterus tracings, with blood specimens from the same cat as in Fig. 12. Ringer's solution was replaced at 45 by the 2nd suprarenal blood specimen (without asphyxia); at 46 by the 4th specimen (asphyxia); at 47 by the 3rd specimen (without asphyxia). Specimens were diluted with 16 volumes Ringer's solution. Ringer's solution was replaced at 50 by "adrenalin" in jugular blood (1:1,600,000); and at 51 by "adrenalin" in jugular blood (1:800,000). The "adrenalin" was added to the undiluted blood in the concentrations mentioned, the mixtures being then diluted with 16 volumes Ringer's solution before application to the segment. (Reduced to one-half.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

flow through the suprarenals and without quantitative determinations of the amount of epinephrin liberated per unit of time, were not suitable for testing the influence of afferent nerves. Up to the present, however probable it may seem that the epinephrin-secreting mechanism can be affected reflexly, no experimental demonstration that this occurs has been given.

It is the same with asphyxia. Anrep(*b*) (1912) stated that he obtained with asphyxia reactions on the denervated limb similar to those elicited by

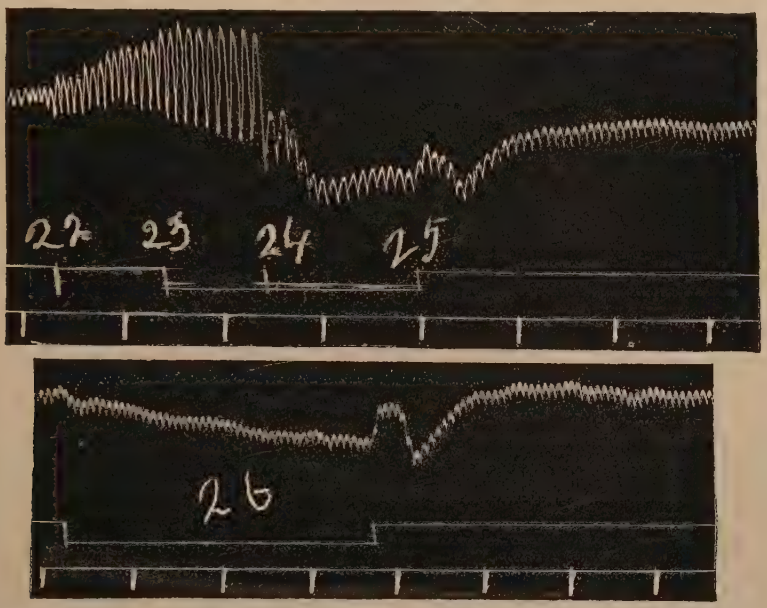

Fig. 14. Blood pressure tracing from a cat. Asphyxia began at 22, stopped at 24. Cava pocket closed to collect suprarenal blood at 23, opened at 25. 26, control pocket experiment without asphyxia. The rise of pressure on opening the pocket is somewhat greater in the control experiment, corresponding to the somewhat longer time during which it was kept closed. If asphyxia had stimulated the output of epinephrin the rise in the asphyxia experiment would have been greater. Line of zero pressure moved up 45 mm. (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

stimulation of sensory nerves, and he interpreted them in the same way, as indicating an augmented output of epinephrin during asphyxia. Pearlman and Vincent have been unable to confirm v. Anrep's observations. They saw no influence of asphyxia upon the denervated limb reaction, which, in any case, for the reason already mentioned, could not be accepted as evidence of a quantitative increase in the epinephrin output. The same is true of the observations of Cannon and Hoskins with the catheter method. Stewart and Rogoff(*a*) (1916-17), using a direct quantitative method (assay of suprarenal vein blood on rabbit's segments (Figs. 12 and 13)), were unable to demonstrate any definite effect of asphyxia upon the rate of output. Nor were they successful with the method of

auto-assay by means of blood-pressure tracings either in the cat (Fig. 14) or in the dog (Fig. 15). Gley and Quinquaud(*e*) found that in prolonged

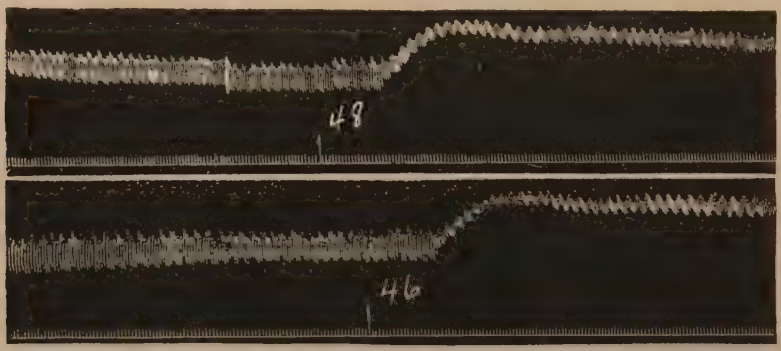

Fig. 15. Blood pressure curves from dog. At 46, a cava pocket which had been closed for 3 minutes was released. At 48, a cava pocket which had been closed for 3 minutes during asphyxia was released. Asphyxia was stopped more than half a minute before the pocket was opened. There is no essential difference in the two curves. Time trace, seconds.

asphyxia a marked increase in the concentration of epinephrin in the blood of the suprarenal vein occurs. But this is simply because the blood flow is correspondingly reduced, the output being unchanged. The central

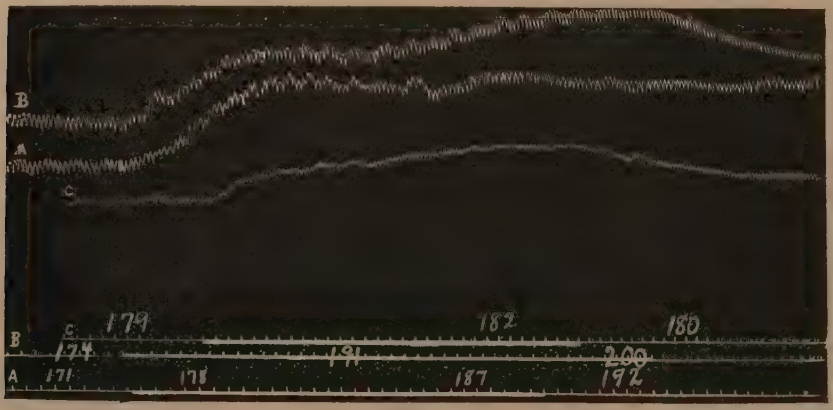

Fig. 16. Blood pressure curves from a cat after section of the vagi and excision of the stellate ganglia. The right suprarenal had been removed and the left suprarenal denervated 34 days previously. *A*, sciatic stimulation before and *B*, after excision of the remaining (already denervated) suprarenal; *C*, after subsequent section of the remaining (right) splanchnic. The numbers show the pulse rates. Decided acceleration of the heart was caused by stimulation of the central end of the sciatic both before and after removal of the left suprarenal. Accordingly this could not have been due to increased epinephrin output. When the blood pressure was diminished by section of the only intact splanchnic nerve the reaction practically disappeared. Time trace, seconds. (Reduced to three-fifths.) (After Stewart and Rogoff, *Am. J. Physiol.*)

nervous mechanism controlling the epinephrin secretion is accordingly not easily stimulated by asphyxia, at least in anesthetized animals. Whether

in animals dying in asphyxial convulsions the spinal epinephrin secretory mechanism, like the spinal motor mechanisms, would be excited so much as to cause a marked increase in epinephrin output is unknown, as it is difficult to collect blood for a satisfactory assay when the flow is greatly slowed.

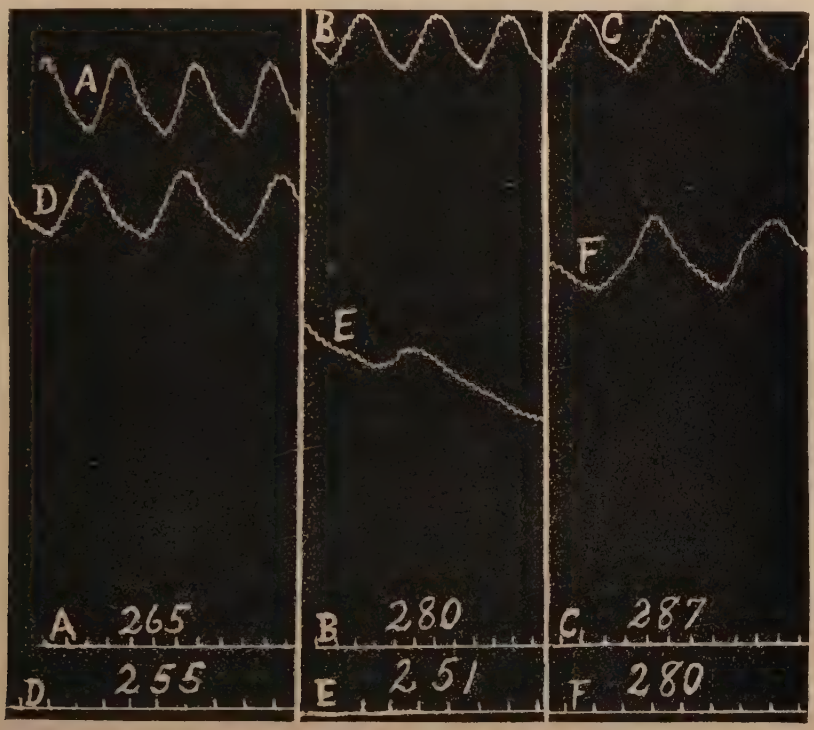

Fig. 17. Blood pressure tracings from cat after section of vagi and excision of stellate ganglia. *A*, before asphyxia; *B*, a portion just before the end, and *C*, a portion commencing 18 seconds after the end of a 45 second period of asphyxia, before tying off all the blood vessels of the suprarenals. The preliminary dissection had already been made and ligatures placed in position. *D*, before asphyxia; *E*, a portion just before the end of asphyxia, and *F*, a portion commencing 27 seconds after the end of a 45 second period of asphyxia, after the suprarenal vessels had been tied off. The numbers give the pulse rates and show that the acceleration of the denervated heart associated with asphyxia was quite as great after elimination of the suprarenals as while they were discharging epinephrin. Accordingly the acceleration caused by asphyxia is not due to increased output of epinephrin from the suprarenals. Time trace, seconds. (After Stewart and Rogoff, *Am. J. Physiol.*)

Cannon's(*e*)(1919) experiments on the heart, assumed to be isolated from the central nervous system by section of the vagi and excision of the stellate ganglia (in cats), do not throw any light upon the question whether it is possible to demonstrate an augmented epinephrin output due to sensory stimulation, asphyxia, or emotion. For it has been shown by Stewart and Rogoff(*t*)(1920) that the reaction upon which he relies, acceleration of the heart, does not depend upon increased epinephrin output

and can be well obtained after removal of the suprarenals or suppression of the output of epinephrin from them (Figs. 16 and 17).

Action of Drugs upon the Epinephrin Output

Apart from the effects of directly stimulating or dividing the splanchnic nerves, or other portions of epinephrin-secretory nervous mechanism, the one way in which decided changes in the epinephrin output have been unequivocally demonstrated up to the present time has been by certain drugs. Strychnin causes a marked increase in the output (up to 10 or 12 times the initial value). This increase is not transient,

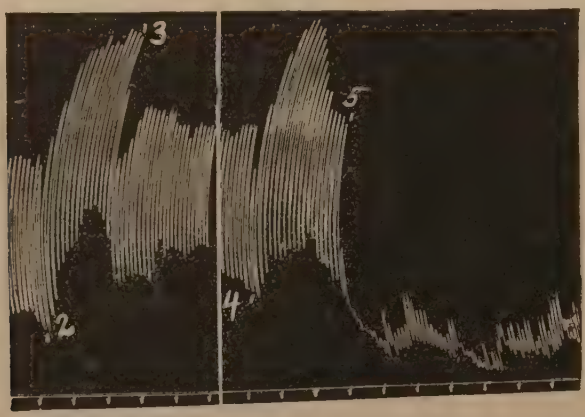

Fig. 18. Intestine tracings. At 2 and 4, Ringer's solution was replaced by indifferent (jugular) blood from a dog, and this at 3 by a specimen of blood from the suprarenals collected before the administration of strychnin; at 5 by a suprarenal blood specimen, collected 3 minutes after strychnin. The blood specimens were diluted with 3 volumes Ringer's solution. Although the blood flow for the latter specimen was somewhat greater than for the specimen obtained before strychnin its epinephrin concentration was more than 10 times greater, as shown by curves not reproduced, and the output of epinephrin was not less than 11 or 12 times the initial output. (Reduced to one-half.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

but persists for a considerable time. Although no attempt was made to continue the experiments until it had completely subsided, a notable augmentation was, as a rule, still found an hour and a half after intravenous injection of the drug, and indeed the action, particularly with the smaller doses, may go on increasing during the experiment. With subcutaneous administration the same effect is produced. Doses of strychnin, probably within the therapeutic range, and which cause little or no exaggeration of reflex excitability, are capable of producing a considerable increase in the rate of output of epinephrin (Fig. 18). In spite of the greatly increased output of epinephrin induced by strychnin there is no evidence that the epinephrin store of the suprarenals is distinctly diminished even by the prolonged action of the drug in large and repeated doses. The

accumulation of epinephrin in the glands is, therefore, accelerated as well as its liberation. As already mentioned, the action is well obtained after section of the cord anywhere in the cervical region, but not after division of the efferent secretory path (splanchnics, etc.). It is, therefore, a central action (on the thoracic cord). Indications were found in some experiments that the state of prolonged augmentation of the rate of output, which constitutes the principal action of the drug, may be preceded by a transient diminution, best seen with the smaller doses and with subcutaneous administration, presumably because with the larger doses and with intravenous injection the augmentation of the output comes on so rapidly as to mask any preliminary decrease (Stewart and Rogoff, 1919(*l, m*). The increase in epinephrin output produced by the intravascular injection of small volumes of concentrated salt solutions (sodium carbonate), accompanied by symptoms of a general excitation of the bulbospinal centers, is probably due, like the strychnin increase, to excitation of the central epinephrin secretory mechanism.

The action of nicotin is, speaking generally, the converse of the strychnin effect. Dale and Laidlaw observed that certain reactions, which are elicited by this drug on the non-pregnant uterus of the cat and in the eye after removal of the superior cervical ganglion, are modified when the experiment is made under such conditions that epinephrin can no longer reach these structures from the suprarenals. They explained the difference by the hypothesis that the nicotin action is in part due to a stimulation of the suprarenals to increased liberation of epinephrin. Gley(*b*)(1914) concluded that the rise of blood-pressure caused by nicotin in dogs with the spinal cord and bulb destroyed is practically due entirely to the increased outpouring of epinephrin. But such a rise of pressure as he saw (*e.g.*, from less than 30 mm. to 140 mm. of mercury in a dog) is far too great to have been caused by any increased output of epinephrin due to nicotin, and was undoubtedly largely due to excitation of the sympathetic ganglion cells on the vasomotor path (see Langley, 1918(*b*)).

Cannon, Aub and Binger, stated that "injection of nicotin in small amounts (3.5 to 7.5 mgm. in cats) results in augmented suprarenal secretion," which is evident in samples of blood obtained 3 or 4 to 10 or 12 minutes after administration of the drug. It is impossible, however, by the method used (collection of blood by a catheter from the inferior vena cava above the level of the suprarenal veins) to arrive at any conclusion as to the effect of the drug upon the rate of output of epinephrin. For changes in the rate of the blood flow were not taken account of, and it is to be expected that the concentration of epinephrin in the suprarenal blood and, therefore, in the caval blood above the suprarenal veins, may be increased at some stage after the injection of such doses of nicotin, owing to the diminution of the rate of blood flow associated with a marked and prolonged fall of blood-pressure succeeding the brief rise. But such an

increase of concentration is always observed when the blood flow in the cava is slowed from any cause whatever, provided that the epinephrin output continues unchanged, or is diminished less than the rate of the blood flow.

It was demonstrated by Stewart and Rogoff(*n*)(1919) that the predominant and by far the most durable action of nicotin, whether administered intravenously or hypodermically, upon the epinephrin output is a depressant or paralyzing action. The maximum diminution of the output is rather rapidly reached and then there is a more gradual recovery,

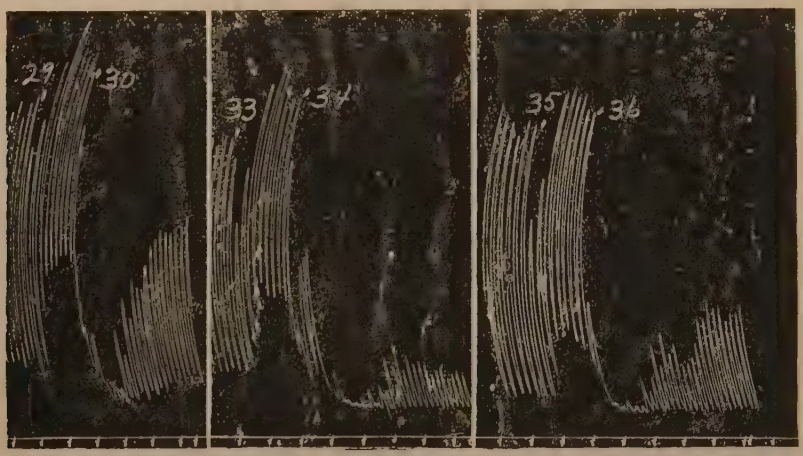

Fig. 19. Intestine tracings. At 29, 33 and 35, Ringer's solution was replaced by venous blood collected after injection of nicotin into a cat; and this at 30 by venous blood to which was added "adrenalin" to make a concentration of 1:660,000; at 34 by a suprarenal blood specimen, collected immediately after injection of nicotin; at 36 by venous blood to which was added "adrenalin" to make a concentration of 1:330,000. All the blood specimens were diluted with 3 volumes Ringer's solution (the "adrenalin bloods" after adding the "adrenalin"). From these and other curves it was shown that the suprarenal specimen had an epinephrin concentration of fully 1:300,000, corresponding to an output of 0.002 mgm. per kgm. per minute, or 20 times the output represented by a specimen taken before the administration of nicotin. (Reduced to one-half.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

which, when the dose is not too large, proceeds until the original output is approximately attained. At the time of maximum depression no epinephrin at all may be detected in the suprarenal vein blood. The depressant action is preceded by a transient stage of excitation, lasting as a rule not longer than from half a minute to less than a minute (Fig. 19). In this stage the rate of epinephrin output is markedly increased (from 2 or 3 to 10 or 15 times the original output, or even more). With intravenous injection of the drug the transient augmentation of the output begins practically at once. In some of the experiments there was evidence that the latent period could not have exceeded a few seconds. The brief stage of excitation passes rather abruptly into the much more durable stage of depression (Figs. 20, 21). The changes in the rate of epinephrin

output are roughly parallel to the changes in the blood-pressure caused by nicotin, indicating that when the sympathetic ganglion cells on the efferent vasomotor path are being stimulated or depressed, a corresponding stimulation or depression is being exerted on the efferent suprarenal secretory path. The transient augmentation of the epinephrin output may be associated with an increase in the concentration of epinephrin in the suprarenal vein blood much beyond the maximum seen with the slowest blood flow in animals simply anesthetized with ether, morphin, or urethane (Fig. 19) so that epinephrin may even be detected in the serum by the colorimetric test of Folin, Cannon and Denis. The strychnin augmentation of the output has not been observed to be associated with any distinct increase in the normal maximum concentration (something like 1:500,000 in the serum of suprarenal vein blood, assayed with rabbit segments) so long as the connection of the thoracic cord with the upper parts of the central nervous system remains unbroken. But when strychnin is administered after section of the cervical cord the increased epinephrin output may be associated with extremely high concentrations of epinephrin (as much as 1:100,000 or even more in the suprarenal blood). A hypothesis which would explain this is that a center exists in some part of the central nervous system above the level of the thoracic cord which exerts an inhibito-regulatory influence upon the output. The transient preliminary diminution in the output caused by strychnin may be due to excitation of this mechanism, the subsequent increase being brought about by stimulation of the thoracic spinal mechanism.

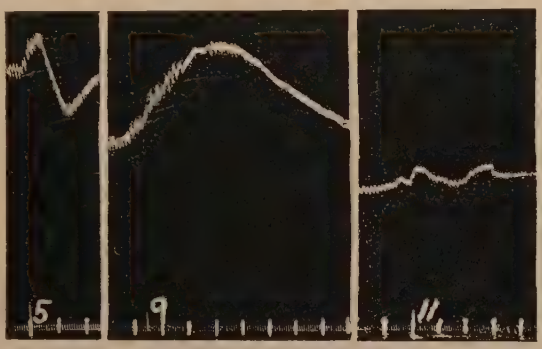

Fig. 20. Blood pressure tracing from a cat. At 5, a two minute cava pocket (before injecting nicotin) was released; at 9, a two minute pocket, during the period of closure of which was injected 1 mgm. nicotin, was released; at 11, a two minute pocket (seven minutes after the nicotin injection) was released. The output of epinephrin was obviously increased at 9 and depressed at 11. Zero line corresponds with time trace and is moved up 30 mm., and the figure then reduced to two-thirds. Time trace shows 10 second intervals. (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

Curare in doses sufficient to paralyze the skeletal muscles of the cat markedly depresses the output of epinephrin from the suprarenals.

It was stated by Ehrmann (*b*) (1906) that atropin and pilocarpin cause no alteration in the quantity of epinephrin in the blood of the suprarenal veins. He refers only to the concentration of the epinephrin. He did not take account of possible changes in the blood flow, and his method

(the Meltzer-Ehrmann reaction with the frog's eye) is not an adequate one for assaying epinephrin in blood. The conclusion that atropin does not diminish the output of epinephrin has nevertheless been confirmed by subsequent workers (Tscheboksaroff(*a*), Popielski(*a*) (1916), Stewart and Rogoff(*x*)). Pilocarpin, according to Tscheboksaroff(*a*) is also without effect, and Stewart and Rogoff (*x*) came to the same negative conclusion, on the basis of quantitative experiments by the rabbit intestine segment method. Dale and Laidlaw, however, have stated that pilocarpin causes a

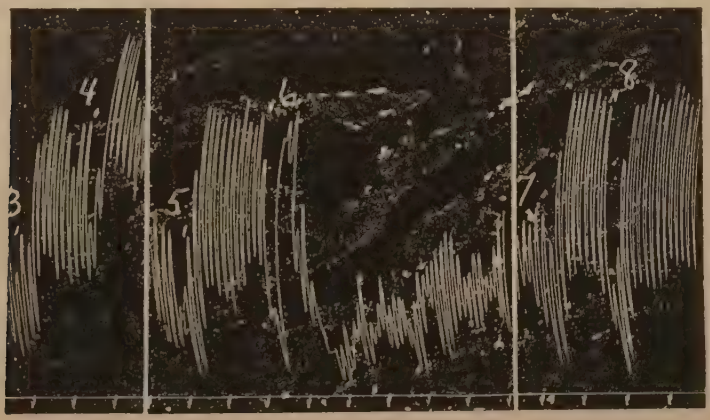

Fig. 21. Intestine tracings. At 3, 5 and 7, Ringer's solution was replaced by jugular blood and this at 4 by the fourth suprarenal specimen (collected one minute after injection of nicotin); at 6 by the third suprarenal specimen (collected immediately after injection of nicotin); at 8 by the eighth suprarenal specimen (collected seventeen minutes after nicotin injection). All the blood specimens were diluted with 3 volumes Ringer's solution. Since the third specimen was collected with a blood flow quite as great as that for the fourth, the figure shows that the output for the third must have been much greater than for the fourth. The detailed assay showed that the output for the third specimen was more than 9 times as great as the initial output before nicotin. The fourth specimen and also the fifth gave no inhibition with the intestine segments, showing a marked depression of the output at this time. At the time the eighth specimen was obtained the output had recovered to approximately the initial value before the nicotin injection. (Reduced to two-thirds.) (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

marked increase in the rate of output, which in one experiment was as much as 0.02 mgm. per minute for the cat, probably 30 times the average output found by Stewart and Rogoff in cats and a greater output than they ever observed even with strychnin or nicotin. The concentrations given by Dale and Laidlaw are also extremely great, as much as 1:100,000 for the blood. The serum would, therefore, have easily given a positive reaction with the Folin colorimetric test. It is difficult to see how an increase of this magnitude could have been missed in Tscheboksaroff's experiments made with the reliable blood-pressure method, or in Stewart and Rogoff's observations made with the both reliable and sensitive rabbit intestine method. Dale and Laidlaw point out that the splanchnic was cut in Tscheboksaroff's observations and not in their own. But it is

hard to understand how this could explain the difference in result, since Dale and Laidlaw observed that section of the splanchnics after the injection of pilocarpin did not interfere with the augmented secretion of epinephrin, and Stewart and Rogoff(*x*) did not cut the splanchnics.

According to Tscheboksaroff(*a*) physostigmin increases the epinephrin output. This was confirmed by Stewart and Rogoff(*w*) who observed an increase (to 10 times the initial output). The action is a central one. Strophanthin has no clearly demonstrable or constant effect (Stewart and Rogoff(*p*) 1919), although some increase was deduced by Richards and Wood(*a*)(1914-15) from observations made by the catheter method on vena cava blood.

Functions of Epinephrin in the Body

The facts that a measurable amount of epinephrin is constantly passing into the blood stream, that this amount reckoned in proportion to the body weight varies but little in different animals and under a variety of experimental conditions, and that the epinephrin output is completely under the control of the nervous system strongly suggest that it must exercise some function in the body. It is true that the epinephrin, which in the blood plasma of the suprarenal veins rarely attains a concentration exceeding 1:500,000 and with ordinary blood flows is usually only a fifth of this or less, is diluted probably 100 to 200 times at least before reaching the lungs. Even if no loss of epinephrin is suffered in the pulmonary circulation, as is probable from Elliott's(*b*) experiments (1904), the plasma can hardly reach the systemic arteries under ordinary conditions with a greater concentration of epinephrin than 1:250,000,000 to 1:500,000,000, corresponding to 1:400,000,000 or 1:500,000,000 to 1:1,000,000,000 for the blood. This agrees fairly well with the approximate estimate of Trendelenburg(*e*)(1915) of the vasoconstricting power of freshly drawn citrated blood from the rabbit's carotid when tested on the frog perfusion preparation. Although this method is exceedingly sensitive there is always the possibility that some part of the constrictor effect may be due to the vasoconstrictor substance developed from the platelets. But in these careful experiments Trendelenburg seems to have controlled this factor as well as is possible. He considers, however, that the true epinephrin content of the arterial blood may be even less than 1:1,000,000,000. In passing through the capillaries practically all the epinephrin disappears even when by continuous infusion of epinephrin into the arteries the concentration in the arterial blood is raised to a value much above the normal. All the statements in the literature purporting to show measurable contents of epinephrin in the peripheral venous blood are erroneous, and are based upon faulty methods. For example Fränkel professed to find by the rabbit's uterus segment method a definite content of epinephrin in normal human serum, which was increased in Graves' disease but not

in chronic nephritis. He reports that in a case of Graves' disease he found a concentration of 1:400,000 in the venous blood, which, according to the best available data, would imply a concentration in the suprarenal vein blood of probably at least 1:1,000 or 1:2,000. This is entirely out of the question. He also asserts that he was able to detect epinephrin (1:20,000,000 or more) in *all* specimens of *normal* human blood.

Cannon and de la Paz stated that in cats frightened by a barking dog so much epinephrin was poured out that the femoral vein blood gave a distinct epinephrin reaction with the intestinal strip. Batelli(*d*) concluded that normal dog's serum contained 1:10,000,000 to 1:20,000,000 "adrenalin," an absolutely impossible result. Schur and Wiesel's(*a, c*) observations on the mydriatic action on the isolated frog's eye of serum and urine in various diseases are also entirely valueless. They were justly criticized by Waterman(*a*), Stewart(*c*)(1912), combining the rabbit intestine segment method and the rabbit uterus method, was unable to find any evidence of epinephrin in blood withdrawn by puncture of a vein from patients suffering from various diseases, including Graves' disease and conditions showing arterial hypertonus. Janeway and Park, using Meyer's artery strip method (both coronary artery and peripheral artery, which react in the opposite way to epinephrin), obtained a negative result in normal human citrated blood, and also in blood from a case of chronic nephritis with high blood-pressure.

Small as the concentration of epinephrin may be in arterial blood, there is evidence that it may exert a certain action. Gley and Quinquaud(*e*) indeed stated that they were unable to obtain any reaction indicating the presence of epinephrin even in the blood of the right heart, although a reaction might be given by blood from the inferior cava above the adrenal level. But this is simply because the test employed by them (the rise of blood-pressure caused by injection of the blood into another animal), although a reliable test, is not a particularly sensitive one. It has already been mentioned that when the splanchnic is stimulated, various definite epinephrin reactions are elicited (dilatation of the pupil and retraction of the nictitating membrane of the eye, sensitized by previous removal of the superior cervical ganglion), a characteristic blood-pressure curve with a double peak [2] and acceleration of the heart (Elliott(*c*) 1912; v. Anrep (*a*) Pearlman and Vincent). Here, of course, there is an abrupt increase in the rate of epinephrin output. But there is evidence that the ordinary output also exerts an influence. For example, when the sensitized pupil has been caused to dilate by epinephrin, it comes back more slowly to its original size if the suprarenal circulation is free than if the suprarenal vein blood is prevented from entering the circulation (Stewart and Rogoff(*i*) 1917). This shows that the epinephrin coming off at the ordinary rate

[2] Gley and Quinquaud(*g*) state that the "double peak" is not seen in rabbits and only in some dogs and cats. When present, it is not affected by adrenalectomy, and therefore not due to epinephrin.

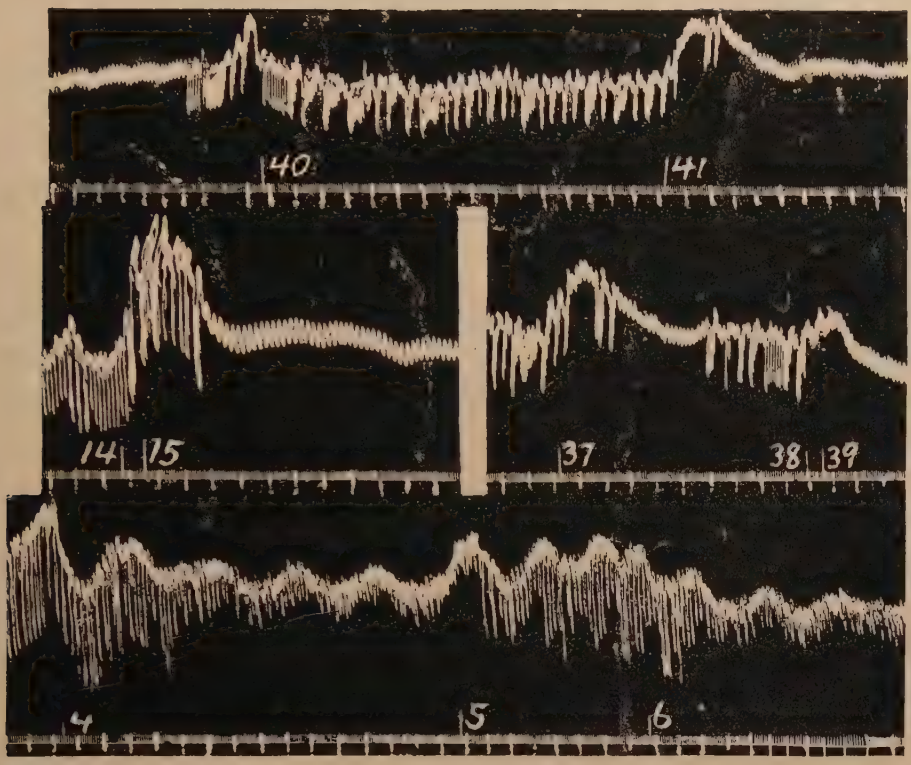

Fig. 22. Blood pressure tracing from a cast showing the effect of exclusion of the naturally liberated epinephrin on a cardiac arrhythmia present at the beginning of the experiment (under urethane), and demonstrating that the epinephrin discharged from the suprarenals exerts an action upon the heart. The vagi were cut at the beginning of the experiment. At 4 the suprarenal blood was excluded from the circulation by closing the cava pocket. At 5 the pocket was released. At 6 the pocket was again closed. The opening of the pocket augmented the irregularity and so did the injection of "adrenalin" at this stage, in such amounts as were used to assay the epinephrin output. A very large amount of epinephrin, on the other hand (0.5 c.c. of a 1:35,000 solution), caused the irregularity to disappear (injection from 14 to 15 in the figure). The same reversal of the original effect was seen at a later stage in the experiment when the pocket was closed off, the irregularity now developing or becoming greater during the period of closure and disappearing, after the usual latent period, when the pocket was opened. At 37, e.g., a pocket which had been closed 3 minutes was opened. At 38 to 39, 1 mgm. of strychnin sulphate was injected, and the irregularity disappeared a little before 40 the irregularity returned and was increased by closing the pocket at 40. After 3 minutes, the pocket was opened at 41 and the irregularity disappeared completely for 2 or 3 minutes. The changes could have nothing to do with any effect of the abstraction of the small quantity of blood collected in the pocket on the filling of the heart. The zero line, coincident with the time trace (seconds and 10-seconds), has been moved up 42 mm. for observations 4 to 6; 40 mm. for observations 14 and 15; and 20 mm. for observations 37 to 41. The finer details of the irregularity in the curve have been somewhat obscured in the reproduction. (After Stewart and Rogoff, *J. Pharm. & Exper. Therap.*)

must have been a factor in maintaining the dilatation. Certain cardiac irregularities have been observed to be modified in a striking manner when the adrenal blood was shut off or allowed to enter the circulation (Fig. 22)(*q*). This indicates that the ordinary epinephrin output was in these cases exerting an action upon the heart. There is a suggestion that the slowing of the heart rate when, after previous section of the vagi, the accelerantes are cut, may be more constant and more marked when the output of epinephrin from the suprarenals has been interfered with before section of the heart nerves than when it is being discharged at the ordinary rate. When the experiment is done in the reverse order, the extrinsic nerves of the heart being first severed, removal of the suprarenals is very commonly followed by a slowing of the pulse, in which the loss of the ordinary epinephrin output may be a factor (Cannon(*e*) 1919; Stewart and Rogoff(*t*) 1920). It is quite true that the artificial injection of such quantities of epinephrin as are ordinarily liberated from the suprarenals can produce only insignificant effects upon the circulation compared with the effects produced through the cardio-regulative and the vasomotor nerves. And there is no reason to believe that even when stimulated to the highest pitch, as by excitation of the splanchnics or by strychnin, the direct action of epinephrin in raising the blood-pressure can never be more than quite subordinate, in comparison with the action of the nervous system. It does not follow that its action is negligible, whether it be regarded as a factor of safety whose full weight, small as it may be, when thrown into the scale in adverse circumstances in which the nervous mechanism is crippled, may turn the balance, or as a sensitizing influence which under normal conditions intensifies the nervous action. The question might be asked whether epinephrin is not a survival, now without much significance in the higher animals, from a stage of development in which hormones carried in the circulation performed some of the functions of the nervous system, which became more and more predominant, as a much more rapid vehicle of communication, as development proceeded. It may be that functionally epinephrin is more important in some lower vertebrates than in mammals. For example, Redfield's (*c*) observations on a lizard, the horned toad, indicate that in the changes in the color of the skin epinephrin may play a part in producing constriction of the melanophore pigment.

It may be taken as certain that whatever functions epinephrin may perform they are not of such a nature that the abrupt suppression of the epinephrin output of the suprarenals causes any gross and obvious change. All the best evidence is to the effect that the blood-pressure remains practically unaltered for a time when the suprarenal veins are carefully clipped. There is not necessarily any fall of pressure when the glands are carefully tied off or excised under anesthesia, or at any rate the pressure curve does not show greater variations than in animals under similar conditions in which the epinephrin discharge is proceeding. (For

evidence, see preceding chapter.) Stewart and Rogoff have often observed a slight fall of pressure when the cava pocket is closed off so as to exclude the suprarenal blood from the circulation. But any direct share which the epinephrin may take in maintaining the normal blood-pressure must be insignificant, and even when the rate of output is much increased by stimulation of the nervous mechanism, e.g., by strychnin, no effect at all comparable in magnitude with the effects ordinarily produced by the vasomotor mechanism can be elicited. This is true even when the suprarenal blood is collected for some minutes and then released. In the present position of our knowledge any claim that the epinephrin liberated from the suprarenals exerts or can exert an obvious, striking and easily demonstrated action upon any function of the body must be considered almost as suspect. It is essential that the quantitative aspect of the epinephrin output be kept steadily in mind in considering this question. For if enough epinephrin be injected into an animal reactions of great magnitude can, of course, be elicited.

Quite recently Gley and Quinquaud(*f*)(1919) have again demonstrated that epinephrin does not directly play a part in maintaining the arterial pressure, since ofter removal of the suprarenals the pressure does not fall, at least during several hours. They have repeated the experiments of Strehl and Weiss, mentioned earlier in the article, which have often been quoted as proving a marked fall of blood-pressure on occlusion of the left suprarenal vein (after previous removal of the right gland). These experiments are a good illustration of the fact that considering the magnitude of the epinephrin output any *large* effect alleged to be due to its suppression or increase is suspicious. The French authors show conclusively that practically no change of pressure occurs, and trace the results of Strehl and Weiss to technical errors. There is no evidence that in conditions associated with a low blood pressure (shock) there is any attempt at compensation by an increase in the epinephrin output (Henderson, Prince and Haggard; Stewart and Rogoff(*r*), 1919; Bedford, 1917). (Fig. 23).

Although no immediate effect on the blood-pressure may be shown on suppressing the epinephrin output, it has been supposed that epinephrin may exert a function in activating or increasing the irritability of the sympathetic system including the vaso-constrictor and cardio-augmentor fibers or of the intermediate link (myoneural junction) between them and the muscular fibers (Elliott(*b*) 1905). Gautrelet and Thomas(*h*) stated, in support of this hypothesis, that after removal of both suprarenals there is a diminution of the direct and reflex excitability of the sympathetic nervous system. They noted a remarkable alteration in tne psychical condition: rats which before the operation were wild and attempted to bite were quite tame and subdued after it. This is quoted here because there is a tendency in much of the literature to emphasize a supposed rôle of

epinephrin in reactions associated with the expression of the emotions. For all this in the opinion of the present writer there is no foundation.

Stewart and Rogoff(*e*)(*s*)(1917, 1919) were unable to observe any difference in the behavior of cats, dogs and monkeys after interference with the epinephrin output, or in the case of rabbits after removal of the suprarenals. Of course animals, if wild or frightened at first, became tame after the operation and as they grew accustomed to their surroundings. But it would require a lively imagination to connect any change of this

Fig. 23. Intestine tracings. At 3, 5, and 7, Ringer's solution was replaced by jugular blood (from a dog), and this was replaced at 4 by a suprarenal blood specimen, collected after 1 hour of exposure and manipulation of the intestines, the blood pressure being 68 mm. of mercury; at 6 by a suprarenal specimen, collected before exposure of the intestines, with blood pressure 90 mm. of mercury; and at 8 by a suprarenal specimen, collected after 2 hours and 20 minutes' exposure of the intestines, the pressure being 55 mm. of mercury. All the blood specimens were diluted with 3 volumes of Ringer's solution. The detailed assay did not show any sensible difference in the rate of output in the different specimens, the increasing concentration in the latter specimens being due simply to a correspondingly diminished blood flow as the pressure continued to sink. (Reduced to one-half.) (After Stewart and Rogoff, *Am. J. Physiol.*)

kind with the loss of epinephrin. Hoskins and Wheelon (1914), who completely ligated the suprarenals in dogs, were unable to confirm the finding of Gautrelet and Thomas in regard to the depression of excitability of the sympathetic system. Hoskins(*f*)(1915), however, observed in dogs, from 1 to 8 days after removal of one-half to seven-tenths of the suprarenal tissue, that the pressor reaction to nicotin was diminished. The reaction to adrenalin was not similarly affected. As is pointed out by Hoskins, it cannot be concluded from these observations that the depression of the irritability of the sympathetic system is specifically related to the loss of the suprarenal substance, still less to diminution in the epinephrin output. Elliott found no change in decapsulated cats till the animals were moribund, when nicotin caused only a slight rise of pressure.

Gley and Quinquaud,(*b*)(*c*)(*d*)(*e*) in a series of papers, have shown conclusively that epinephrin does not play the rôle attributed to it in maintaining the tonus of the sympathetic. In support of their attitude of skepticism they have shown: (a) that excitation of the peripheral end of a splanchnic nerve produces its habitual effect on the arterial pressure after double epinephrectomy or after ligation of the two lumbo-adrenal veins; (b) that reflex excitation of the splanchnics after these operations has the usual effect upon the circulation; (c) that the excitability of the cardio-accelerator and cardio-inhibitory nerves remains the same; (d) that the result of excitation of the vasomotor centers by asphyxia is identical before and after these operations.

There is no good evidence that epinephrin from the suprarenals regulates diuresis, although it has been shown that some anastomosis may exist between the suprarenal circulation and the veins of the capsule of the kidney. This was described by Tuffier and Lejars in the human subject, where, of course, the anatomical relations of the suprarenal and kidney are closer than in lower animals. According to Cow (1914) epinephrin may, under certain conditions, pass from the suprarenals by this route, a conclusion which finds support in certain observations of Stewart and Rogoff. Experiments by Cannon and Nice and by Gruber(*b*) have been interpreted as showing that the threshold stimulus of fatigued muscles can be lowered by the action of such amounts of epinephrin as are given off from the suprarenals in response to stimulation of the splanchnic nerves. As has been pointed out by Gruber, however, the improvement in the fatigued muscles is due, in part at any rate, to the improved blood flow associated with the increased blood-pressure, although he is emphatic in asserting that increased blood flow is not the sole factor. No difference has been observed in the resistance to fatigue of decapsulated and normal rats (Boinet)(*b*) or of cats deprived of the greater part (as much as 5/6 or 7/8) of the suprarenal tissue and normal cats (Stewart and Rogoff(*y*)).

Epinephrin and Blood Sugar Content.—In no part of the subject has the lack of attention to the quantitative relations of the epinephrin output led to greater errors than in the numerous investigations which have sought to connect the suprarenal medulla with the regulation of the carbohydrate metabolism and especially of the content of dextrose in the blood. The idea that increased epinephrin output might play a part in increasing the blood sugar content and, therefore, in causing glycosuria, was originated by Blum(*b*) who suggested that the piqûre glycosuria, discovered by Claude Bernard in 1855, might be of the same nature as the glycosuria caused by injection of suprarenal extract. The same question has been raised in regard to other experimental glycosurias (and hyperglycemias), e.g., those caused by anesthetics, by asphyxia, by emotional excitement, etc. A very large number of papers have been published maintaining the indispensability of the suprarenals for the production of these conditions and

not a few denying that the suprarenals are essential. Thus, Mayer(*a*) stated that after excision of the suprarenals in rabbits, piqûre caused no glycosuria in the 8 hours following the operation. Borberg(*a*) obtained the same result, but only in one rabbit. Kahn(*a*), in two rabbits which had survived removal of the suprarenals at two operations, saw no glycosuria after piqûre, and this was confirmed by Kahn and Starkenstein, and by Biberfeld(*b*), who, however, admits that observations on sugar in the urine are unsatisfactory in the absence of blood sugar estimations. On the other hand, Wertheimer and Battez(*a*)(*b*) obtained distinct glycosuria in the cat (14 times out of 43) and in the dog (9 times out of 35) on performing piqûre after removal of both suprarenals, necessarily in acute experiments.

As regards investigations in which the blood sugar was estimated, the results are also contradictory. Thus, Jarisch concluded that, after denervation of the suprarenals in rabbits, piqûre did not cause any increase in the blood sugar. But his experiments were vitiated by the fact that the glycogen store of the liver was in every case so low that there could not have been any certainty that in normal animals a distinct hyperglycemia would have resulted from piqûre. The conclusion of Freund and Marchand that piqûre causes an increase in blood sugar after removal of the suprarenals in rabbits, although certainly correct, could not be deduced from their results, as the piqûre was made only two or three hours after removal of the suprarenals and under anesthesia, which itself causes hyperglycemia. Confusing as these results were, the question is nevertheless not a difficult one to settle and the astonishing lack of uniformity in the results is due almost entirely to the neglect of essential conditions. Two main ways of approaching the question are theoretically open: (*a*) the estimation of the output of epinephrin under the action of the factors inducing the experimental hyperglycemia (or glycosuria), in order to show whether this can be sufficiently great to permit the introduction into the blood of the necessary excess of epinephrin as determined by artificial injection; (*b*) study of the sugar content of the blood (or urine) in the absence of the suprarenals or after interference with their epinephrin secretion. The first method of approach might seem the most direct, but it has been little used. Such results as have been obtained on the rate of output of epinephrin in ether narcosis and asphyxia are quite unfavorable to the view that epinephrin plays any sensible rôle in the production of the hyperglycemia. Thus in etherized cats Stewart and Rogoff(*e*)(*s*) found an average output of 0.0002 mgm. epinephrin per kgm. of bodyweight per minute, and this was not increased in asphyxia. Now Underhill was unable to produce glycosuria in non-narcotized rabbits even when he administered epinephrin at approximately 20 times this rate for more than 2½ hours by continuous infusion into a vein, although he found, in confirmation of Ritzmann, that these large doses caused some glycosuria in urethanized rabbits. The statement of Waterman and Smit, repeated

later by Waterman(*c*), that after piqûre epinephrin can be demonstrated in the general venous blood is erroneous. The Meltzer-Ehrmann (frog's eyeball) reaction employed by these observers is useless for this purpose, as has been well pointed out by Schultz(*b*). Even in the arterial blood and with a much more sensitive method (the frog perfusion preparation) no epinephrin has been detected after piqûre (Kahn(*c*), v. Brücke, Negrin y Lopez).

The proper way to settle this question is to collect blood from the suprarenal veins and to assay its concentration in epinephrin by a reliable method. This has been attempted by Kahn(*d*)(1912) and by Quinquaud, (1915), who convinced themselves that there was some increase in the concentration of epinephrin in the blood of the suprarenal veins after piqûre. But the experiments were few and not very consistent, and in the absence of exact measurements of the rate of blood flow they cannot be accepted as proof of an increased output. A diminished blood flow would be not unlikely to be present some hours after piqûre and this of itself would entail an increased epinephrin concentration if the output had remained unaltered. There is in any case no proof and little probability that if an increase had been demonstrated in the epinephrin output, it could ever be great enough to cause a demonstrable increase in the blood sugar content. By an indirect and not very satisfactory method Trendelenburg and Fleischhauer reached the conclusion that the rate of discharge of epinephrin is not increased by the diabetic piqûre.

The second method of testing the question, inducing the conditions associated with hyperglycemia (or glycosuria) after the suprarenals have been interfered with so as to render an increase in the epinephrin output impossible, has been much more extensively employed. Although many observers have come to the conclusion that in the absence of the suprarenals the experimental hyperglycemias in question do not occur, this is due solely to the fact that essential conditions were neglected. Of these the most important are: 1. An increase in the sugar content of the blood and not the appearance of sugar in the urine should be the test. It is well known that little or no urine may be secreted in acute experiments, after such operations as epinephrectomy and piqûre, and the absence of glycosuria has then no value. 2. The glycogen store must be adequate to permit of a decided hyperglycemia. Negative results cannot otherwise be accepted. The only sure way is to estimate the liver glycogen. 3. Only animals which have completely recovered from the effects of the operation practiced to eliminate the epinephrin output of the suprarenals should be used, e.g., rabbits which have survived double epinephrectomy, and cats after removal of one suprarenal and section of the nerves of the other. 4. At least one major splanchnic nerve should be left intact. It is quite unphysiological to sever the splanchnics on both sides when the question is to decide whether the suprarenals are essential for the production of a

hyperglycemia. For the innervation of other organs, especially the liver, is thus crippled. A negative result obtained after double splanchnotomy could have no value in this connection. 5. In experiments on piqûre the floor of the fourth ventricle should be exposed under local anesthesia.

It has been shown by Stewart and Rogoff(*g*)(*k*)(*u*) (1917-18, 1920) that, when the above mentioned conditions are fulfilled, the experimental hyperglycemias under discussion are well obtained in the absence of epinephrin discharge from the suprarenals. The so-called epinephrin hypothesis of these hyperglycemias should, therefore, be abandoned. Whatever the mechanism of their production may be, the suprarenal bodies are not essentially concerned. It has not been proved that the epinephrin liberated from the suprarenals even sensibly facilitates the production of any of the hyperglycemias, although some observers (Macleod and Pearce) believe they have obtained a certain amount of evidence that this may be the case. If a slight influence of this kind really existed it would be very difficult in such observations to disentangle it from the variations due to conditions which cannot be controlled. This is the main reason for the contradictory statements in the literature in regard to the existence of the so-called emotional hyperglycemia. Some writers (Shaffer, e.g.) have convinced themselves that emotional hyperglycemia is so easily produced in the ordinary laboratory animals that it is impossible to obtain "normal" sugar percentages unless great precautions are adopted to prevent excitement. Others (Ross and McGuigan) have found it difficult to convince themselves that a real emotional hyperglycemia exists. A survey of the available data (Stewart and Rogoff(*g*), 1917) indicates that in any case there is a fundamental distinction between the hyperglycemia associated with asphyxia, anesthesia or piqûre, which is well established and easily verifiable, and "emotional hyperglycemia," the existence of which is asserted by some authors on the basis of small and inconstant differences in the blood sugar content, which other writers consider to fall within the limits of variation of the normal. There is no evidence that "emotional hyperglycemia," if it exists, is at all related to the epinephrin discharge from the suprarenals. The possibility may be admitted that different species of animals, perhaps different individuals of the same species, may vary in their susceptibility to emotional excitement as regards changes in the blood sugar content. If this were so, man might be expected to be more susceptible than lower animals. Cannon, Sholl and Wright saw glycosuria regularly in cats as a result of emotional excitement, and Cannon(*a*) (with Smillie and with Fiske) found it in some of the students of a class subjected to the stress of an examination, and in football players.

Several of the writers on the problem of the possibility of producing experimental hyperglycemia (and glycosuria) after removal of the suprarenals have raised the question of the ability of the liver to form or to

store glycogen in the absence of these glands. Schwarz, for instance, has stated that although the livers of epinephrectomized rats, after feeding with dextrose or cane sugar, contain considerable quantities of glycogen, they are practically free from glycogen when carbohydrate is supplied in the form of starch as in feeding "semmeln." Kahn and Starkenstein asserted that even when milk and oats were given in addition, glycogen was not stored except in traces. It was pointed out by Stewart and Rogoff(*k*) (1918) that these negative results were due to failure to observe essential conditions, e.g., allowing a sufficient time after the operation for the animal to recover completely. They showed that the formation and storing of glycogen in the liver is not essentially affected by removal of both suprarenals in rabbits and rats, or by removal of one suprarenal and section of the nerves of the other in cats. Kuriyama(*b*) also was unable to find any evidence that the epinephrin output of the suprarenals influences the glycogen store.

There is no evidence that the rate at which glycogen is transformed into dextrose or the rate at which dextrose is oxidized in the organism (Lusk and Riche) is influenced by epinephrin liberated from the suprarenals. The blood sugar content after removal of both glands lies within the normal range (Nishi, Stewart and Rogoff et al.). The too frequently quoted statement of Porges that a marked hypoglycemia exists in dogs after suprarenalectomy, a conclusion previously reached by Bierry and Malloizel, has no significance as death very soon follows the operation in dogs.

The Question of the Indispensability of Epinephrin.—That epinephrin is not indispensable for life and health is certain. Cats, dogs and monkeys have been shown to live indefinitely in good health after excision of one suprarenal and section of the nerves of the other, an operation which, as previously mentioned, either abolishes the output of epinephrin or reduces it to a small fraction of the normal. The animals may lose weight for a week or two and possibly to a greater degree than after an operation of similar severity, not involving the suprarenals. But they soon recover and, if not fully grown, put on weight and behave in all respects, so far as has been observed, like normal animals. The epinephrin output may be so much reduced that even with a very slow flow no epinephrin reaction may be obtained with rabbit intestine (and uterus) segments which would detect a concentration corresponding to even 1/1,000 of the ordinary output (Fig. 24). It is possible that after a certain period some regeneration of epinephrin-secretory fibers may occur. This would not of course explain survival if suprarenal epinephrin was indispensable, even if regeneration were complete. But even after months the output, after section of the nerves, is only a small fraction of the normal. For instance, in a monkey (Macacus rhesus) the right suprarenal was excised and the nerves of the left cut. The animal was allowed to live more than 9½ months and was

then sacrificed, being in perfect health, to permit estimation of the epinephrin output. It was found that the concentration of epinephrin in the suprarenal vein blood was no more than 1:75,000,000 and the output no more at most than 1/10 of the normal. According to Langlois(*a*) about 1/6 to 1/11 (Whipple and Christman say 1/6) of the total mass of the suprarenals must be left in dogs to prevent death, and according to Biedl, about 1/8 in cats, dogs and rabbits. It seems certain that when cats and dogs die after removal of 9/10 of the suprarenal substance, even if medulla and cortex are not removed in the precise proportion in which they exist

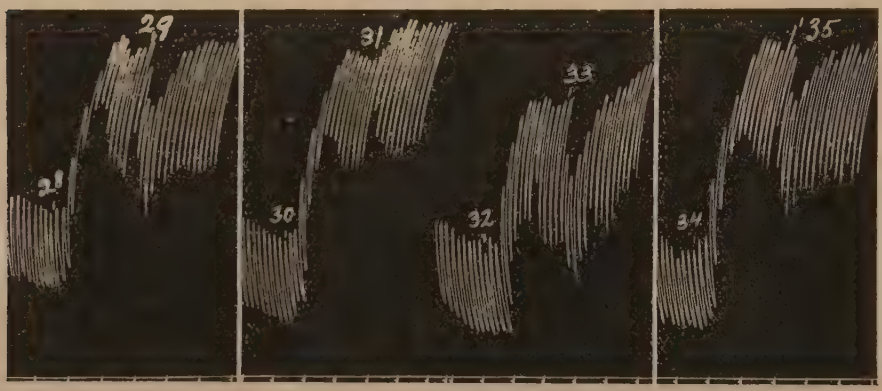

Fig. 24. Intestine tracings. Blood specimens from a dog in which the right suprarenal had been excised and the nerves of the left cut 25 days previously. At 28, 30, 32 and 34, Ringer's solution was replaced by indifferent blood, and this at 29 by indifferent blood to which was added "adrenalin" to make a concentration of 1:500,000,000; at 31, by a specimen of suprarenal vein blood; at 33, by indifferent blood to which was added "adrenalin" to make a concentration of 1:650,000,000; and at 35, by indifferent blood to which was added "adrenalin" to make a concentration of 1:800,000,000. All the blood specimens were diluted with one volume Ringer's solution (the "adrenalin" specimens after adding the "adrenalin"). The segment was unusually sensitive. Numerous additional observations were made with this and other specimens of blood from the suprarenals, but no evidence was obtained that any of them contained a detectable content of epinephrin. It was calculated that the output could not have been as much as 0.0000002 mgm. per kgm. per minute, i.e., not 1/1000 of the normal output. (Reduced to one-half.) (After Stewart and Rogoff, *Am. J. Physiol.*)

in the gland, which could only happen by chance, they do not die because of deficient epinephrin liberation from the suprarenals. More than 20 per cent of rabbits, indeed, and 50 per cent of rats, survive the total removal of both suprarenals. The explanation commonly given is that accessory suprarenals, consisting of cortical tissue, are especially liable to occur in these animals. All the best evidence goes to show that it is the cortex (or interrenal tissue) and not the medulla (or chromaphil tissue) of the suprarenals which is indispensable to life. The cortical tissue alone undergoes hyperplasia, when a deficiency is created by removal of a considerable part of the tissue. Thus, when one adrenal is removal the cortex of the other hypertrophies. This is especially evident in the rabbit. Statements in the literature that the chromaphil tissue may also undergo

compensatory hyperplasia have no sufficient foundation. Only the cortical tissue can be successfully grafted. Granting that the cortex is essential to life, the question may be raised whether the chromaphil tissue is not also essential. Biedl asserts that because of the existence of chromaphil tissue outside of the suprarenal (extracapsular chromaphil tissue), it is never possible to create a physiological deficiency of epinephrin by removal of the suprarenals. Zuckerkandl(*a*) found constantly in the human embryo and new-born child a pair of chromaphil bodies in the retroperitoneal space at the origin of the inferior mesenteric artery. Kohn(*b*) described in the dog and other animals a considerable strip of chromaphil tissue, which Vincent, (*d, g*) who extended Kohn's work, designates as the "abdominal chromaphil body." It was shown by Biedl and Wiesel that extracts of Zuckerkandl's bodies, and by Vincent that extracts of the chromaphil bodies of the dog cause the same effect upon the blood-pressure as extracts of the suprarenal medulla. Fulk and Macleod confirmed the existence of epinephrin in the retroperitoneal chromaphil tissue in a large number of animals and in man by the action of extracts upon rabbit intestine and uterus segments. Other considerable groups of chromaphil cells exist, such as those in the carotid body, and there are scattered chromaphil cells in the sympathetic ganglia, although in the higher mammals these are not numerous. J. F. Gaskell(*a*)(1912-13) has brought forward some evidence that the chrome-staining tissue at the bottom of the vertebrate scale, in Petromyzon, also contains epinephrin. Recently he has extended his studies to invertebrates(*b*)(1919), and states that the chromaphil cells in the ganglia of the leech contain epinephrin. It is, of course, extraordinarily difficult to obtain sufficient material for a satisfactory test, but in the one experiment made, an extract of 400 leech ganglia gave some inhibition of the cat's virgin uterus.

It may be concluded with some confidence that the extracapsular chromaphil tissue contains epinephrin. But it must not be assumed without proof that this is given off to the blood. The denervated suprarenal contains epinephrin and speedily accumulates a full load, but if section of the epinephrin-secretory fibers is complete, it does not pass into the circulation. Everything depends, therefore, upon the innervation of the extracapsular chromaphil cells. It seems probable that if they do liberate epinephrin, this liberation is controlled by nerves, and Kahn(*e*) (1912) states that by means of the frog perfusion method he has shown that epinephrin is given off to the blood by the abdominal chromaphil body of the dog. The experiment, however, is very difficult to carry out without fault. Most of his curves do not show any very great difference between serum from the caval blood and serum from the abdominal ganglion (chromaphil body), although one or two do. The possibility of massage is perhaps not excluded. Kahn makes an interesting calculation as to the relative content of epinephrin in the abdominal chromaphil body

and the suprarenals in the dog, and arrives at the result that even in the dog it is only a small fraction of the suprarenal store (1/12 to 1/30). The whole mass of the extracapsular chromaphil tissue put together, according to him, is insignificant compared with the suprarenal medulla. This has an important bearing upon the question whether the suppression of the epinephrin output of the suprarenals is compatible with life because epinephrin is not essential, or merely because sufficient epinephrin is still liberated from the extracapsular chromaphil tissue. In the opinion of the writer all the evidence is in favor of the view that epinephrin is not essential. Vincent(*d*)(1917), for instance, points out that from the relatively large size of the chromaphil body in the dog, this animal might be expected to be more resistant to extirpation of the suprarenals than other animals if the chromaphil tissue were essential. But the dog does not survive the operation, whereas the white rat, in which Vincent failed to find any traces of "extra-suprarenal chromaphil tissue," is the most resistant of all the laboratory animals. In the monkey, also, no chromaphil bodies have been recognized with certainty. Yet the monkey is not affected by interference with the epinephrin output of the suprarenals. It has further been noted (Stewart and Rogoff, (*u*) 1920) that if the diffuse chromaphil tissue is under the control of nerves in respect of any output of epinephrin, as is to be supposed by analogy with the suprarenal medulla, the output would be greatly interfered with by operations often practiced and not incompatible with life, e.g., section of the splanchnics or appropriate section of the dorsal spinal cord, operations which also greatly interfere with the output of epinephrin from the suprarenals and which have sometimes been successfully combined with operations for the extirpation of one or (in rabbits) of both suprarenals.

The Epinephrin Store of the Suprarenals.—The quantity of epinephrin in the suprarenals is best estimated by the colorimetric method of Folin, Cannon and Denis, from the depth of the blue color given by an extract with a solution of sodium phosphotungstate. Other colorimetric methods have also been employed, e.g., that of Seidell(*a*)(*b*). It can also be well estimated from the rise of pressure produced by injection of known amounts of an extract into a cat with the brain and the upper part of the cord destroyed, according to the method of Elliott(*c*)(1912). Roughly speaking the amount of epinephrin, expressed as base, present in the suprarenals in most animals, when not placed under conditions which are known to cause diminution of the store, is about one one-thousandth of the moist weight of the glands. As it is confined to the medulla the proportion in the medulla is of course much higher, in many animals at least one per cent of the moist weight. According to Elliott the load is practically identical in each of the two glands. As was shown by Elliott in the cat, if the nerves of one gland be cut and a day or two be allowed to elapse to permit the store to be replenished, a deficiency in the load of the

innervated gland as compared with its denervated fellow is caused by the action (for some hours) of narcotics, like morphin, ether, chloroform, urethane; of β-tetrahydronaphthylamin, and other drugs; and of certain bacterial toxins.

The diminution in the epinephrin store produced by morphin in the cat has nothing to do with the apparent psychical excitation expressed by the incessant restless movements, dilated pupils and staring eyeballs associated with the action of the drug in this animal. For a precisely similar depletion is seen in the still innervated gland in the dog, in which the narcotic action of morphin is typically displayed. And the intense excitement produced by the natural antipathy of dog and cat causes no depletion of the epinephrin store of the innervated as compared with the denervated gland even when the excitement is continued for several hours (Stewart and Rogoff(*c*), 1916).

Some writers seem to assume that any condition which causes depletion of the epinephrin store produces this effect by augmenting the rate of epinephrin output. This is erroneous. The store represents the balance between epinephrin formed and epinephrin liberated, and a diminution in the store may be due either to diminished upbuilding or to increased discharge. In the case of ether and some other anesthetics, there is no evidence of any stimulation of the output, and it is probable that the depletion of the store of epinephrin in the innervated gland is due, mainly at any rate, to the steady liberation of epinephrin at approximately the ordinary rate while the new formation of epinephrin is interfered with. If no epinephrin at all were formed under the influence of these drugs, its continued liberation for 5 or 6 hours, without augmentation in the rate of output, would reduce the store by approximately 50 per cent, and the depletion actually observed is of this order of magnitude. It is not known in what way drugs like β-tetrahydronaphthylamin cause depletion of the epinephrin store, whether by increasing the output or by diminishing the formation of epinephrin, or possibly by a combination of both actions. Morphin has been shown to increase the output in cats (to as much as ten times the original rate.) But this cannot be the sole cause of the diminution in the epinephrin store. For in dogs the increase in output is trifling in comparison, or there is no definite increase. As already remarked, strychnin, which greatly augments the output, does not affect the store (Stewart and Rogoff).

Before leaving this subject it must be remarked, to prevent misapprehension, that it has been clearly demonstrated by Elliott(*c*)(1912) that epinephrin can be formed and stored in the suprarenal after as complete denervation as is practicable. Of course, some nerve fibers running in on the blood vessels, etc., may escape. The denervated gland, as already stated, regains its normal load, somewhat depleted by the anesthesia and operation, in the course of a day or two, and maintains it thereafter.

When this point has been reached it must be assumed that further formation in the denervated gland practically ceases, since if there is any "spill" into the blood when the epinephrin-secretory nerves are eliminated it is so small as to escape detection, in some cases even by rabbit intestine segments, which would have been capable of responding to concentrations of epinephrin corresponding to one one-thousandth of the ordinary output.

There is nothing in this inconsistent with the view that although a deficiency in the store itself constitutes a "stimulus" to new formation of epinephrin till the saturation point has been reached, a "quick-charging" nervous mechanism exists which hastens epinephrin formation, and that when the liberation of epinephrin is accelerated through excitation of the nervous system, the auxiliary mechanism which speeds up the formation of epinephrin is normally excited at the same time. In animals dead of infections of various kinds, the suprarenal protected by section of its nerves has been seen to have a markedly greater store of epinephrin than its fellow, but this is not true of all infections. In man Comessatti(*b*) obtained very variable results in an investigation of the epinephrin store in 70 patients dead of various diseases, including chronic nephritis. As he justly remarks, such observations have a very limited value. Lucksch(*d*) found that in animals poisoned with diphtheria toxin, the epinephrin disappeared altogether or in great part from the suprarenals, as shown by the great diminution in the pressor effect of extracts (cf. Tscheboksaroff(*b*), 1911). Ritchie and Bruce confirmed this, showing that in guinea pigs affected by diphtheria toxemia running a slow course the suprarenal medulla is devoid of epinephrin, whereas in hyperacute infection death occurs before the depletion becomes total. Schmorl and Ingier, however, saw no diminution in the epinephrin content of the suprarenals in man in the majority of cases of acute infection, especially diphtheria. They employed the colorimetric method of Comessatti.

That little or no epinephrin should be found in the suprarenals in Addison's disease (Oliver and Schäfer, Ingier and Schmorl et al.) has no special pathological significance. A diseased suprarenal is very likely to lose its epinephrin store. The edema of the suprarenal which is apt to result from trauma in its immediate vicinity, especially in the rabbit, is associated with great diminution in the epinephrin store, which is regained after a time when the edema has subsided (Stewart and Rogoff(*c*), 1916). Cramer(*c*) has described histological changes in the suprarenal medulla under the influence of severe cold and other conditions. Some observers have endeavored to show an interrelation between the suprarenal medulla and other endocrine tissues by determining whether changes occur in the amount of the epinephrin store in various experimental conditions. Thus, Herring(*a*)(*b*) stated that thyroid feeding caused an increase and thyroidectomy a decrease in the epinephrin store. For the reason already mentioned, this would have no direct bearing upon what is after all the

important question, whether the thyroid influences or can influence the rate of output of epinephrin. But Kuriyama(*a*)(*b*) has been unable to detect any definite effect produced by thyroid feeding upon the epinephrin store when the ordinary variations in its amount are taken into account. Gley(*a*)(1914) arrived at a similar negative result as to the effect of thyroidectomy and of removal of the pancreas(*c*)(1915).

There is, however, no reason to doubt that when certain conditions as to dosage and duration of feeding are observed, the suprarenals may hypertrophy (and the epinephrin store increase) as Herring has maintained, in confirmation of the observations of E. R. and R. G. Hoskins(*a*). But there is nothing specific about this increase in size of the suprarenals since similar hypertrophy is found in other organs, including the pancreas (E. R. Hoskins, Kojima) after thyroid feeding. The risk of deducing a special physiological relationship between the thyroid and the suprarenals merely because hypertrophy of the suprarenals has followed thyroid feeding is illustrated by the fact that removal of the thyroids may also be associated with suprarenal hypertrophy (Gley(*a*), Carlson, Stewart and Rogoff(*z*)). These glands, indeed, seem to vary much in size, like the thyroid, and under many physiological and pathological conditions. Their hypertrophy in pregnancy (Guiyesse(*b*), Watrin(*a*), *et al.*) and still more during lactation (Verdozzi(*a*)) seems to be a normal physiological event, but its significance is unknown. C. A. Stewart(*b*) observed a progressive increase in the size of the suprarenals in young rats, underfed for long periods. Jackson(*b*) has also described changes in the suprarenals of rats during inanition. McCarrison(*c*) saw enlargement of the suprarenals associated with inanition and also with a scorbutic diet, and Vincent and Hollenberg have confirmed his findings. Many infections and intoxications are accompanied by suprarenal enlargement (Langlois(*c*), Porak(*b*), *et al.*), although enlargement due to edema (and congestion) has not always been discriminated from true hypertrophy. Mulon and Porak found that in animals employed for the production of antibodies of various kinds the cortex was hypertrophied. Porak says that the largest suprarenals seen by him were in rabbits repeatedly injected with sheep's erythrocytes for the production of anti-sheep serum for the Wassermann test in the Paris municipal laboratory.

Statements in the literature to the effect that extracts of thyroid, pancreas, liver, testes, kidneys, and of other organs increase the output of epinephrin (Gley and Quinquaud(*a*) *et al.*), in so far as they are not based upon a faulty technic, are simply due to a failure to distinguish between an increased concentration of epinephrin in the blood coming from the suprarenals and an increased output of epinephrin per unit of time. It is well known that such tissue extracts cause a fall of blood-pressure and, therefore, a slowing of the blood flow. The concentration of epinephrin

must accordingly be increased even if no change has occurred in its rate of output.

The elaborate theory of the reciprocal relations of the endocrin organs originated by Eppinger, Falta and Rudinger gains no support from such experimental observations as have been made either upon the epinephrin store or the epinephrin output. Gley and Quinquaud(*a*) very naturally express astonishment at the ease with which these theories gained a considerable degree of acceptance without ever having been subjected to a direct experimental investigation, and surmise that this was due to the fact that they are supported especially by "investigations concerning the nutritive exchanges." Lusk and Riche showed that not one of the statements as to the supposed rôle of epinephrin in metabolism and its action upon the endocrin organs (pancreas and thyroid) upon which the theory was based is true, and conclude that the theory is not tenable in any of its particulars. The subject of the reciprocal action of the endocrin tissues is dealt with elsewhere in this work. But it may be pointed out here how improbable it is that so many tissues and organs of such diverse structure and ancestry should form an autonomous physiological system, all the members of which are linked together in a specially intimate manner, merely because they have been rather clumsily classified by the superficial morphological character that they are of glandular nature, but do not possess ducts. Even this is not a thoroughgoing distinction in the case of the thyroid.

Nothing has been said as to the supposed "disintoxicating" function of the adrenals, their power of neutralizing toxic substances produced in metabolism, because nothing is known. The relative constancy of the epinephrin output and its strict regulation by the nervous system are as compatible with the view that epinephrin is a poison which must be gradually got rid of, and whose concentration in the blood must not rise above a certain maximum, as with the view that it is a substance exercising a useful function, which could not be adequately performed if the output were permitted to sink below a certain minimum.

The Emergency Function of the Suprarenal Medulla . . . . . *W. B. Cannon*

Introduction—Review of the Positive Evidence—Evidence that Suprarenal Secretion Is Induced by Sensory Stimulation—Evidence that Suprarenal Secretion Is Induced by Asphyxia—Evidence that Suprarenal Secretion Is Induced by Excitement—Discussion of the Methods Yielding Negative Evidence—Interpretation of the Function of the Suprarenal Medulla.

The Emergency Function of the Suprarenal Medulla

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Introduction

A point of prime importance in the functioning of the suprarenal medulla is its subjection to central nervous influences coming to it by way of the splanchnics. With a variety of methods, in the hands of various investigators, proof has been brought that artificial stimulation of the splanchnic nerves will induce secretory activity in the medullary portion of the suprarenal gland, and that in consequence epinephrin is increased in the blood. Thus the fact is now securely established that there exists in the body a mechanism by which this endosecretory gland can be made to discharge its products promptly into the circulation.

The splanchnic nerves belong to the sympathetic division of the autonomic system, that portion of the nervous organization of an animal that is brought into action during great emotional stress and during asphyxia and painful stimulation. Under such conditions, from one end of the body to the other, there is evidence of nervous discharges *via* the sympathetic. In the cat, for example, the hairs rise on the head, back and tail, the activities of the stomach and intestines are inhibited, and there is widespread vasoconstriction. With such general involvement of the sympathetic division in activity do the splanchnic fibers distributed to the suprarenal medulla participate? Is there discharge, or increased discharge, of epinephrin in these circumstances?

The answer to these questions is important for several reasons. First, because epinephrin by itself and in very small amounts can induce important changes in the body; second, since epinephrin has the same effects on the viscera as do sympathetic nerve impulses, it would, if specially secreted in times of stress, coöperate with those impulses; third, special secretion would justify the existence of acknowledged secretory nerves; and fourth, since function is associated with action, the circumstances inducing a special secretion of the suprarenals would properly suggest their normal functions.

In two papers published in 1911, Cannon, in collaboration with de la Paz and with Hoskins, brought forward evidence that the suprarenal medulla was stimulated to secrete by emotional excitement, by "pain" and by asphyxia. In a series of papers which followed these first two, experiments were described showing that suprarenal secretion was serviceable in lessening muscular fatigue (Cannon and Nice; Gruber(*d*)) and in accelerating coagulation of the blood (Cannon and Mendenhall). An interpretative paper (Cannon(*a*), 1914) pointed out that excitement, pain and asphyxia were conditions which in natural existence would commonly be associated with struggle, and that the visceral changes, including suprarenal secretion, which accompany these three states, would be useful in great muscular effort. This interpretation presented a new view of the function of the sympathetic division of the autonomic system and of the suprarenal medulla in important bodily adjustments.

Within the past few years both the evidence on which the foregoing interpretation was based and the interpretation itself have been seriously questioned. In an extensive series of papers, Stewart and Rogoff have reported apparently careful quantitative studies on the rate of suprarenal discharge, and have drawn the conclusions that the discharge is continuous, that in any animal it is approximately constant, and that the supposed variation is dependent on the rate at which the blood flows through the lumbo-suprarenal veins (1917(*f*)). They found no increase of secretion in pain (1917(*i*)), asphyxia (1917(*a*)), or emotional excitement (1917(*g*)). More recently Gley and Quinquaud(*e*)(1918) have also examined experimentally suprarenal secretion and have come to the decision that epinephrin is not secreted in sufficient amount to be carried effectively to the organs on which it may act, and that therefore no true physiological "adrenalinemia" exists. There is then a sharp difference between the views put forth by Cannon and his coworkers and the ideas supported by these later investigators. In the following account the evidence for and against special secretion will be presented and discussed.

Review of the Positive Evidence

Evidence That Suprarenal Secretion is Induced by Sensory Stimulation.—In the original tests Cannon and Hoskins made use of rhythmically contracting segments of rabbit intestine suspended lengthwise in a glass cylinder through which oxygen was passed. The segment, when not surrounded by the blood to be tested, was bathed in Ringer's solution. The test blood, the cylinder and the fresh Ringer's solution were all kept at body temperature in a common bath. The blood to be tested was taken before and after the experimental procedures by passing a cathether through a nick in the femoral vein into the iliac and thence into the inferior vena

cava anterior to the entrance of the lumbo-suprarenal veins. A thread tied tightly around the catheter marked the point to which it was inserted and permitted reinsertion to the same point in subsequent sampling of the blood. The position of the catheter opening, which was at one side, was kept constant by attention to the position of the knot in the thread. Thus both the control blood and the blood after stimulation were taken as exactly as possible from the same region. Under these circumstances normal blood removed before stimulation of the central end of the sciatic nerve caused no inhibition of the rhythmically contracting intestinal segment, whereas that removed afterwards produced a marked relaxation. After various control observations the conclusion was drawn that the suprarenal glands are affected through nervous channels when a sensory trunk is strongly excited and that they then pour into the blood stream their secretion.

The foregoing conclusion was supported a year later by Anrep(*a*), who found that the denervated limb or kidney at first expands but later quickly contracts when the central end of the cut sciatic nerve is stimulated. If the suprarenal glands were removed, or the splanchnic nerves were cut, the the phase of contraction disappeared. Since the organs (limb or kidney) were denervated, the only factor which could cause their contraction in the presence of a rise of general blood pressure must be some agency brought by the blood stream; and since the phenomenon disappeared on exclusion of the suprarenals, the conclusion was drawn that suprarenal secretion, poured out in consequence of reflex stimulation through the splanchnics, produced the observed vasoconstriction. The observations of Anrep on the denervated limb have recently been confirmed by Pearlman and Vincent.

The year following Anrep's studies Levy reported the incidental observation that after both stellate ganglia had been removed and both vagus nerves cut, stimulation of the sciatic nerve occasioned irregularity of the heart. He also noted that excitation of the peripheral end of the cut splanchnic would cause the same cardiac changes, and that they did not occur if the suprarenal gland was removed on the stimulated side. He therefore concluded that on sciatic stimulation the denervated heart was being affected by epinephrin discharged reflexly.

In 1917, Florovsky undertook an investigation of a strange fact previously observed by Ostrogorsky, which was that if the cervical sympathetic and the chorda tympani nerves are severed, and the secretory effect of a dose of pilocarpin is disappearing, sciatic stimulation causes a considerable increase in the flow of saliva. The effect was so striking that he looked for a third nerve to the submaxillary gland but could not find it. Under the conditions described by Ostrogorsky, Florovsky succeeded in producing augmented salivary secretion by stimulating the peripheral end of the cut splanchnic and by intravenous injection of epinephrin.

He also confirmed Ostrogorsky's observation of an augmented flow after sciatic stimulation. This reflex secretion did not occur, however, if both suprarenal glands were extirpated, or if one was extirpated and the vein of the other obstructed, or if both splanchnic nerves were cut. He concluded, therefore, that the anomalous secretion from the denervated submaxillary gland is due to suprarenal secretion resulting from reflex stimulation.

Cannon(*d*)(*e*)(1917, 1919) making use of some incidental observations of previous investigators, suggested the use of the completely denervated heart to demonstrate an increase of epinephrin in the circulating blood. In a cat under urethane, with vagi cut and stellate ganglia excised, stimulation of the central end of the cut sciatic caused the heart rate to increase in some instances as much as fifty beats a minute. Reflex increase of the cardiac rate did not occur or was slight after the suprarenal glands were removed.

The foregoing evidence, involving tests made on blood removed from the body, and tests made in the body on the denervated limb, the denervated kidney, the denervated salivary gland and the denervated heart, are harmonious in testifying to a reflex discharge of the suprarenal glands when a sensory nerve is stimulated.

Evidence That Suprarenal Secretion is Induced by Asphyxia.—In their examination of the effect of asphyxia on suprarenal secretion, Cannon and Hoskins, in 1911, used the same methods that were employed for testing the effect of sensory stimulation. In the course of the examination it was discovered that *extreme* asphyxia would cause a change in the blood which would produce the same effect as epinephrin on the beating intestinal strip, i. e., inhibition, and this even though the suprarenal glands had been carefully removed or the circulation confined to the region above the diaphragm. This observation indicated the necessity for careful control at the time the asphyxial blood was taken. Accordingly, after *moderate* asphyxia, there was removed, from the femoral vein, blood which should serve as a control sample of the systemic venous flow below the entrance of the lumbo-suprarenal veins; and at as nearly as possible the same time another sample was removed from the inferior vena cava at a point anterior to the opening of these veins. This latter blood caused the typical inhibition indicating the presence of suprarenal secretion, whereas the control femoral blood, like the vena cava blood taken before asphyxia, failed to cause inhibition. Through the use of the control, therefore, the presence of an accessory factor, simulating the action of epinephrin, was ruled out. Consequently the conclusion was drawn that asphyxia results in secretion of the suprarenal glands.

In 1912, Anrep(*a*) noted that a decrease in volume of the denervated limb and denervated kidney occurred during asphyxia, in spite of a general rise of arterial pressure, just as he had seen it occurring as a consequence

of sciatic stimulation. This vascular constriction appeared, however, only when the suprarenal glands were connected with the circulation and the splanchnic nerves were intact. When these glands were out of circulation, asphyxia caused some rise of arterial pressure, though less than in the intact animal, but no constriction of the vessels in the denervated limb or kidney. He concluded, therefore, that the suprarenal glands are excited during asphyxia. These observations of Anrep on the constriction of the vessels in the denervated limb were at once confirmed by Itami, who found that it did not occur after transection of the cord. Since the constriction was not due to the direct action of CO_2 on the vessel wall, nor to reaction of the vessels to an increased internal pressure, he interpreted the result as due to increased suprarenal secretion.

In 1914, Gasser and Meek, while making observations on a dog with stellate ganglia removed and the vagi cut, noted, when the animal was asphyxiated for 30 seconds, an acceleration of the heart amounting to 92 beats per minute. Now, under ether anesthesia, the blood vessels of the suprarenal glands were tied. After recovery from the operation, asphyxia lasting 90 seconds caused an acceleration of only 8 beats per minute.

In 1917, Gley and Quinquaud(*c*) found an amount of epinephrin in suprarenal venous blood, obtained during asphyxia, considerably in excess of that obtained when the animal was undisturbed. Using the rise of blood pressure as a test, they determined that from 4 to 8 c.c. of the asphyxial suprarenal blood were equivalent to 16 c.c. of the blood before asphyxiation. In their experiments injection of 20 c.c. of blood from the inferior vena cava, taken above the suprarenal veins after 3 or 4 minutes of asphyxia, caused a rise of arterial pressure from 24 to 45 mm. higher than that produced by injecting an equal quantity of cava blood taken from the same level before asphyxia. Asphyxiation of the cat with the heart completely denervated caused, in Cannon's(*e*) experience (1919), a noteworthy increase in the heart rate, an effect which was not seen after suprarenal extirpation.

The foregoing evidence, which, like that obtained after sensory stimulation, was the result of studies by various observers using a variety of methods, is harmonious in leading to the conclusion that suprarenal secretion is increased by the asphyxial state.

Evidence that Suprarenal Secretion is Induced by Excitement.—In the experiments on the influence of emotional excitement, performed by Cannon and de la Paz in 1911, the methods employed were similar to those used by Cannon and Hoskins. The only differences were that the animals did not receive a general anesthetic and that the catheter was introduced under local anesthesia. Controls were obtained in every instance. As the original records show, after emotional excitement the blood drawn from the inferior vena cava anterior to the opening of the

suprarenal veins repeatedly caused inhibition of the beating intestinal strip, whereas that removed before excitement had no such effect. Since excitement after removal of the suprarenal glands did not yield this result, and since the effective blood lost its inhibitory power when exposed to oxygen (a procedure known to destroy epinephrin), the inference was drawn that suprarenal secretion is stimulated by great emotion.

In addition to these direct observations on the stimulating effect of strong emotion on suprarenal secretion, there were other observations having inferential value. In 1914, Cannon and Mendenhall, after showing that clotting of the blood is hastened by stimulation of the splanchnic nerves, found that great excitement will cause the same effect. The evidence which they brought that injected epinephrin shortens the clotting time, that when the splanchnic nerves are stimulated the suprarenal glands are necessary for the effect, and that excitement induces faster clotting only so long as the splanchnic nerves are intact, was confirmatory of the view that excitement causes suprarenal discharge.

In 1915, Lamson noted that injection of epinephrin would cause a polycythemia, and that emotional excitement, such as fear and rage, would likewise cause it. If an animal was frightened after removal of the suprarenal glands, however, there was no increase in the red count. Lamson observed that asphyxia had the same effect as fright and that removal of the suprarenals prevented the customary increase seen after asphyxiation.

The completely denervated heart can be used as an indicator of suprarenal secretion in testing the influence of emotional excitement just as it is used in relation to sensory stimulation and asphyxia. It is only necessary to take somewhat greater pains in order to keep animals in normal condition after operation. To denervate the heart, the stellate ganglia are first removed under ether with aseptic precautions; later the right vagus nerve is severed below the recurrent laryngeal branch; and still later, the left vagus nerve is cut in the neck. The heart is thus wholly disconnected from the central nervous system and any agency causing an increase in the heart rate must exert its influence through the blood stream, either mechanically or chemically. Electrocardiographic records of the heart rate under these conditions show an increased rate during excitement when the glands are present, and a failure of noteworthy increase when they are absent (Cannon(*e*), 1919). By both direct and indirect testimony, offered by different observers using different methods, the evidence is concordant that emotional excitement is accompanied by increased secretion of the suprarenal medulla.

Discussion of the Positive Evidence

Objection to this evidence of increased suprarenal secretion has been raised by Stewart and Rogoff, who declare that no reliable conclusion can be drawn from it without knowledge of the rate of blood flow.

The Catheter Method. In criticism of the catheter method used by Cannon and Hoskins, they state that the results obtained by it are valid only if the blood flow is assumed to be constant during the whole experimental period; and second, that the method does not permit any judgment on this point (Stewart and Rogoff(*i*), 1917). Thus, if there be a continuous secretion of epinephrin undisturbed by reflex stimulation, as they maintain is the case, there could be an increased concentration only if the blood flow through the suprarenal vessels were retarded. There is another possibility, however, which should be considered. The blood flow through the suprarenal vessels might be increased. Strong sciatic stimulation has a well-known pressor effect. This may be due largely to reflex splanchnic stimulation. But there is no evidence that splanchnic stimulation causes constriction of suprarenal vessels. Indeed, the careful observations of Burton-Opitz and Edwards have shown that stimulation of the splanchnic nerves causes a greater blood flow through the suprarenal vein, a result which Biedl(*b*) had previously noted (1897). With a heightened general blood pressure and at least no constriction of the suprarenal vessels, the blood flow through these vessels must necessarily be increased. Under these circumstances, on the basis of Stewart and Rogoff's argument, the epinephrin would be more dilute rather than more concentrated in the suprarenal blood.

In answer to this consideration they have suggested that the blood from the suprarenals is only a small portion (perhaps 1/100 to 1/200) of the blood passing along the inferior cava, and has, therefore, no sensible influence on the rate of flow in the cava. Because of vasoconstriction they assume this flow to be retarded to a degree which causes a sufficient concentration of epinephrin to evoke typical effects. They have offered no evidence that their assumption is true. On the other hand, with increased arterial pressure, a faster heart rate, and a deepened respiration—such as occur in pain and excitement—a faster flow in the inferior cava would naturally result. Direct study of the blood flow in the inferior cava under experimental conditions has recently been made by Opitz. He has found that both splanchnic stimulation and reflex stimulation from the sciatic nerve (the mode Cannon and his collaborators employed) resulted in a *faster* flow through this great venous trunk. The faster flow in the cava just anterior to the suprarenal veins, that accompanies reflex stimulation, would, of course, be highly unfavorable for demonstrating an increased concentration of epinephrin, if it were true

that suprarenal secretion is constant and unvarying. In consideration of the faster flow the positive evidence which was obtained that epinephrin is actually concentrated in the circulating blood at that point in times of stress shows, definitely, that there is an increased secretion from the glands.

The Denervated Heart. Stewart and Rogoff(*k*) have offered several arguments opposed to the conclusion that effects seen in the denervated heart are satisfactory proof of increased adrenal secretion (1918). These arguments are as follows:

1. They point out that after removal of the suprarenal glands sciatic stimulation still increases the heart rate. That is true. But the amount of increase is much less than when these glands are present. Cannon and Rapport found that with suprarenal connections intact the average acceleration of the denervated heart in 104 observations was 29 beats per minute; and after removal of the glands it was, in 163 observations, only 6 beats per minute. Furthermore, if the hepatic nerves were severed when the suprarenals were excised, sciatic stimulation had no effect or caused an insignificant increase of only 2 beats per minute. And yet with the hepatic nerves cut and the suprarenal connections preserved, reflex stimulation evoked the usual great acceleration of the heart.

2. They state that there is nothing strange about an increase in the rate of the denervated heart when the central end of the sciatic is simulated: "It is obviously dependent upon the better blood flow through the coronary arteries." This statement they do not support with any good evidence. With reference to it, testimony regarding the effects of blood pressure (and, therefore, blood flow) in the isolated heart must be relied upon. Martin, Magrath and Kennedy, MacWilliam, Lehndorff, Knowlton and Starling, and Cannon(*e*)(1919) have reported that the rate of such a preparation is not dependent on the blood pressure, i. e., the rate remains uniform (after suprarenal removal, in Cannon's experiments), although blood pressure is varied through wide ranges. Guthrie and Pike likewise testify that the denervated heart *in situ* does not beat more rapidly with a rise of pressure, *unless the circulation has been stopped* for "comparatively long periods." After the heart has been thus asphyxiated, the rate varies directly with the pressure in the aorta. This condition was not present, however, in our experiments. The explanation of the faster cardiac beat in terms of a better blood flow is therefore not only without support but is abundantly contradicted by competent observers.

3. The third argument offered by Stewart and Rogoff is that the rise of blood pressure, by increasing the rate of blood flow through the denervated heart, increases the *amount* of epinephrin passing in unit time, and the organ responds to the increased amount even without change in the rate of suprarenal secretion. In answering this argument, Cannon(*e*)

checked the rise of blood pressure by thoracic compression while stimulating the sciatic, and permitted the pressure to rise immediately thereafter. The heart rate increased just as much during stimulation as it had in a previous test when no check was applied, and *it did not increase any further when the pressure was allowed to rise.* The heart rate, when fastest, was not near the maximum, and consequently it could have been faster. In commenting on this experiment, Stewart and Rogoff(*t*) argue (1920) that thoracic compression by checking venous return alters the *concentration* of the secreted epinephrin, and consequently the heart is accelerated; and that when the pressure rises, the concentration becomes proportionally diminished, and therefore no change in the rate is seen. For this argument to be sound, it would be necessary to prove quantitatively that checking the venous return did in fact have the effect which is claimed. This was not done. On the other hand, the test has been made by Cannon and Rapport of passing a constant flow of epinephrin into the inferior cava after removal of the adrenal glands, and holding the pressure down during stimulation of an afferent nerve. There was no increase of heart rate. The explanation given by Stewart and Rogoff is, therefore, not sustained by experiment.

4. A fourth argument presented by Stewart and Rogoff, and one which they reiterate frequently, is that afferent stimulation by constricting splanchnic vessels lessens the blood flow through the liver; in consequence the secreted epinephrin contained in the cava blood is less diluted (i. e., more concentrated) than normal and therefore has more stimulating power. So far as the denervated heart is concerned, it is not the concentration in the inferior cava but the concentration in the coronary vessels, which is effective. Recently Cannon and Rapport have tested this fourth argument,—after cutting the mesenteric nerves, tying the carotids, subclavians, and renal vessels, and the aorta and inferior cava below the renal branches, and placing a tight ligature about the inferior mesenteric artery and nerves (referred to later as a "reduced" animal). Thus the possibility of a shift of the circulation was reduced to a minimum. Nevertheless, under light ether anesthesia, brachial stimulation for 30 seconds increased the rate of the denervated heart in 25 instances by an average of 26 beats per minute (in 13 cases more than 30 beats). During stimulation, the changes of blood pressure were insignificant (in 17 of the 25 instances less than 10 mm. Hg) or were only moderate variations *up* or *down.* There was no possibility under these circumstances of any great concentration of secreted epinephrin because of failure of blood to pass through constricted splanchnic vessels, for the nerves which would cause constriction of these vessels had been previously cut. The increased rate could not have been due to "a redistribution of blood," for the possibilities of any considerable redistribution of blood were lacking. The only explanation that appears is that the output of epinephrin was increased.

Another experiment of similar import performed by Cannon and Rapport was that of extirpating the suprarenals and severing the hepatic nerves without lowering blood pressure and without interfering with vascular reflexes. Then a constant stream of epinephrin at the rate declared by Stewart and Rogoff to be "normal" was introduced into the femoral vein. While this flow was continuing uniformly, the brachial nerve was stimulated. The blood pressure rose as usual, but there was no increase in the rate of the denervated heart or at most an increase of two beats per minute. "Redistribution of blood" was thus again proved inadequate as an explanation of the faster rate.

5. According to Stewart and Rogoff(*w*) the denervated heart "has no significance as an indicator of augmented epinephrin output" (1920). Cannon and Rapport found, however, that in a "reduced" animal repeated equal doses of epinephrin, injected intravenously at a uniform rate, repeatedly produced in a given animal the same or nearly the same maximal increases of heart beat, and further, that if the injections differed in rate the increases likewise differed in degree. When the circulation is simplified, as in the reduced animal, the cardiac acceleration is chiefly or wholly dependent on the rate of injection, and is little, if at all, influenced by variations in blood pressure. By matching epinephrin injections with reflex adrenal secretion, it was shown that when the denervated heart in the reduced animal is accelerated between 30 and 42 beats per minute, the output from the suprarenal glands lies between 0.0032 and 0.0037 mg. epinephrin per kilo per minute, i. e., more than ten times the amount (0.00025 mg.) regarded by Stewart and Rogoff as the unvarying normal secretion.

The foregoing considerations reveal evidence which requires further "explaining," if the conclusion is to be drawn that secretion of the suprarenal glands is constant and unvarying.

Discussion of the Methods Yielding Negative Evidence

Since Stewart and Rogoff are alone in their view that there is no marked change in the rate of secretion from the adrenal glands, it is perhaps reasonable to inquire whether the peculiar method which they employed, rather than the various methods used by others, may not have features which would account for the discrepant results.

The method of Stewart and Rogoff. Stewart and Rogoff(*b*) obtained evidence of adrenal secretion by the use of a "pocket" in the inferior vena cava (1916). This pocket was made by clamping the vena cava immediately above the iliacs, then clamping the renal veins, emptying the cava segment by stripping it upwards, and placing a clamp on the vessel above the entrance of the lumbo-suprarenal veins. Any small branches of

the cava segment were tied. The pocket thus formed was allowed to fill with blood from the suprarenal veins, and this blood was either allowed to pass into the general circulation by removal of the clamp on the inferior cava, or was withdrawn and tested outside the body on preparations of rabbit uterus and intestine. The arrangement was modified in the "permanent pocket" by tying splanchnic vessels and shutting off the blood flow in the hind quarters. Experiments performed under these conditions revealed a spontaneous liberation of epinephrin, which was unchanged in amount by sciatic stimulation or asphyxia. A number of conditions pertinent to this method and its results are worthy of consideration.

1. It has long been known that opening the abdomen is attended by splanchnic nervous discharges which inhibit the movements of the stomach and intestines (Bayliss and Starling). Only when these disturbing consequences of operation are eliminated do the movements occur. The blood vessels of the mesenteries also become constricted (Henderson); indeed, there is evidence of general vasoconstriction, splanchnic and somatic, in consequence of abdominal section and intestinal manipulation (Erlanger, Gesell and Gasser). In other words, all parts of the abdominal viscera, vascular and gastro-intestinal, are specially innervated by the splanchnics when the abdomen is opened and its contents handled. In view of the typically diffuse distribution of sympathetic impulses, it is highly improbable, to say the least, that the fibers supplying the suprarenal medulla are alone excluded from increased activity. In a number of cases of low rate of the denervated heart not yet published, the rate has been seen to go up promptly when the abdomen was opened.

2. In a series of cases reported by Cannon(*e*)(1919), sciatic stimulation and primary asphyxia, in cats under urethane anesthesia, were usually ineffective in accelerating the isolated heart, if the abdomen had been opened and the mesentery denervated. Stewart and Rogoff(*t*)(*w*)(1920) report that they have had no difficulty in causing acceleration of the denervated heart after opening the abdomen. It may be that the depth of anesthesia is, in addition to laparotomy, an important factor in checking reflex effects, for recently Cannon and Rapport have been able, after opening the abdominal cavity, to cause commonly acceleration of the denervated heart by sciatic stimulation, if light ether anesthesia was maintained. There is some question, however, whether the conditions of Stewart and Rogoff's experiments permitted the abdominal reflexes involving the suprarenal glands, that would be present in animals with abdomen intact.

3. In some of their experiments with use of the cava pocket, Stewart and Rogoff have reported blood pressures. These pressures have fallen in different cases as low as 40, 29, and even 20 mm. Hg (1916(*b*)). As is well known, abdominal operations and repeated opening of the abdominal cavity are likely to be attended by a failing circulation. It is noteworthy that the blood flow into the pocket, in cases where no blood pressure has been

registered, becomes gradually much reduced in the course of time,—e. g., from 2.5 g. to 0.3 g. per minute (1917(*e*))—indicating that the experimental procedure has been lowering the pressure. The very abundant blood supply to the suprarenals, more abundant than in any other organ in the body, according to Neuman, is probably associated with their close dependence on abundance of supply. The reduced flow, therefore, should not be regarded as a condition of little moment.

4. The average output of the suprarenals per kilo per minute, assayed by eye and blood pressure methods by Stewart and Rogoff was 0.0006 mg. epinephrin; the average output assayed by their use of intestine and uterus segments was less than half this amount (0.00025 mg.). "It is quite impossible," they state, "to explain this difference as due to accidental variations in the rate of output in the animals of the two series. It must, therefore, be concluded that some of the epinephrin is lost when the adrenal vein blood is drawn, in the interval which necessarily elapses, and under the manipulation which the blood necessarily undergoes before it is applied to the segments" (1917(*e*)). If epinephrin is lost through manipulations and delay, may not variations of the output, reflexly induced, be minimized or extinguished by the time the tests are made?

5. The foregoing considerations are offered as possible factors in accounting for the difference between the conclusions of Stewart and Rogoff and all other investigators of suprarenal secretion. Stewart and Rogoff(*w*) have argued that their method alone gives reliable data, because it is quantitatively correct (1920). If, however, the fundamental circumstance of their experiments, the operative procedure, is so disturbing as to induce a pathological state, the quantitative method does not report on a physiological process. And if an undetermined amount of epinephrin is regularly "lost" in the manipulations incidental to testing it, the assays are valueless. These are the central considerations in the differences which have arisen. To account for the positive effects reported by all other investigators, Stewart and Rogoff have assumed, without proof to justify their assumption, that these positive effects are due to shifts of the circulation, with consequent concentrations of epinephrin in the blood. They have then proceeded with quantitative methods giving negative results, and have not applied quantitative methods to learn whether their explanation of the wholly contradictory results of others is correct. Until this is done, the prime circumstances of their method remain questionable.

The Method of Gley and Quinquaud. Gley and Quinquaud(*e*) (1918) removed blood from the inferior cava immediately above the opening of the subhepatic veins and again from the right or left ventricle, in each case after splanchnic stimulation. The blood thus obtained was injected in 20 c.c. amounts into other dogs weighing from 4 to nearly 10 kilos. Only the blood which was taken from directly above the opening of the suprarenal veins caused any rise of pressure in the dog injected. They

conclude, therefore, that the epinephrin present in suprarenal blood after splanchnic stimulation is found neither in the blood of the vena cava above the subhepatic veins nor in the blood of the heart.

In drawing this conclusion Gley and Quinquaud seem to have disregarded the fact that they were, in the first place, taking only a small portion of the secreted epinephrin, which had already been diluted by the blood of the donor, and were then injecting this small portion into the blood stream of another dog, where it would be diluted to a much greater degree.

Gley and Quinquaud declare categorically that secreted epinephrin is not carried by the circulation to the organs on which it acts, and that, if present at all, it is present in a quantity altogether minimal and insufficient to exercise its action. This declaration again is made without due regard to evidence already in the literature. The observations on the denervated limb, on the denervated kidney, on the denervated salivary gland and on the denervated heart, quoted or described above, present evidence that suprarenal secretion may be stimulated by painful impulses, by asphyxia and by emotional excitement, and that the substance secreted under these circumstances not only is carried to the structures on which it acts, but produces on these structures pronounced physiological effects. Until this evidence is definitely proved to be unworthy of acceptance, the conclusion which Gley and Quinquaud have drawn must be regarded as unjustified.

Interpretation of the Function of the Suprarenal Medulla

With the fading out of the view that the suprarenal glands produce some substance which neutralizes toxic material developed in the body, there have been left two main theories to account for the rôle played by the suprarenal medulla in the bodily economy. These are the tonus theory and the emergency theory.

The tonus theory, which has been advocated in the past (Elliott, 1904, 1914(*f*); Biedl, 1913(*f*)) and still receives attention, holds that the function of the secreted epinephrin is to maintain the sympathetic endings in a state of responsiveness to nervous stimulation or in a condition of moderate activity or tone. This view has definitely lost ground in the course of relatively recent researches. A number of investigators have called attention to the depressive effect of small doses of epinephrin (Hoskins and McClure(*b*), Cannon and Lyman). If the smallest dose which will have any influence whatever on the blood vessels induces relaxation of the vessels, it is difficult to understand how the function of the secreted epinephrin could be that of maintaining a state of tonic contraction. Furthermore,

as has been repeatedly noted (Lewandowsky(*c*), Camus and Langlois, Hoskins and Wheelon), removal of both suprarenals does not for some time cause the fall of arterial pressure which naturally would be expected if continued secretion of epinephrin were needed to keep the pressure up; and also stimulation of the splanchnic nerves induces the same rise of pressure after suprarenal excision as before (Gley and Quinquaud(*e*), 1918). From these results the conclusion has been drawn by Hoskins and McClure and by Cley and Quinquaud that the tonus theory is without adequate experimental support.

The emergency theory was presented by Cannon(*a*)(1914) on the basis of studies of suprarenal secretion following stimulation of afferent nerves, asphyxia and emotional excitement. In the papers bearing upon this theory emphasis was repeatedly laid upon the association between suprarenal activity and the activity of the sympathetic division of the autonomic system in such emergencies. Nowhere has the statement been made that secreted epinephrin has a function separate from that of the nerve impulses, except to increase the irritability of fatigued muscles (Cannon and Nice; Gruber(*d*)) and to speed the coagulation of the blood (Cannon and Mendenhall). The idea originally suggesting these studies on suprarenal secretion was that changes in the viscera originally induced by nervous impulses might be continued by circulating epinephrin (Cannon(*b*), 1915). No claim has ever been made that there is at any stage a primacy of epinephrin in the production of physiological or psychological changes seen during strong emotion.

Thus far no reliable evidence has been brought out by any investigator that there is any secretion of the suprarenal glands under quiet, peaceful conditions. Stewart and Rogoff have shown that the cat and the dog will live normally for weeks with one adrenal excised and the other denervated, an operation which may result in no demonstrable flow of epinephrin from the suprarenal vein (1917(*e*)). These observations prove that suprarenal secretion is not a necessity, at least in times of serene existence. There is evidence, however, that epinephrin is secreted in times of great emotional stress and under circumstances which cause pain or asphyxia. The function of the suprarenal medulla is to be looked for under conditions which rouse it to action. Excitement, pain and asphyxia are, in natural existence, commonly associated with violent struggle for self-preservation. Under such circumstances, as has been emphasized in the presentation of the emergency theory, the operation of the sympathetic division of the autonomic system together with the aid which epinephrin affords will muster the resources of the organism in such a way as to be of greatest service to such organs as are absolutely essential for combat, flight or pursuit. The cessation of activities of the alimentary canal; the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart,

the central nervous system, and, at critical moments, the skeletal muscles as well (Cannon(*b*), 1915; Hoskins, Gunning and Berry); the increased cardiac vigor; the quick abolition of the effects of muscular fatigue (Gruber(*d*)), the mobilizing of energy-giving sugar in the circulation (Cannon, Shohl and Wright)—these are the changes which occur when fear or rage or pain causes the suprarenal glands to pour forth an excessive secretion. These changes in the body are, each one of them, directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve; for fear and rage are organic preparations for action, and pain is the most powerful known stimulus to supreme exertion. The organism which with the co-operation of increased suprarenal secretion can best muster its energies, can best call forth sugar to supply the laboring muscles, can best lessen fatigue, and can best send blood to the parts essential in the run or the fight for life, is most likely to survive. Such, it is submitted, is the function of the suprarenal medulla at times of great emergency.

Relation of the Suprarenal Glands to the Circulation . . .
. . . . . *R. G. Hoskins*

Earlier Work on Suprarenal Pharmacology—Locus of Stimulation by Epinephrin—Destruction of Epinephrin in the Body—Effect of Acute Suprarenal Deficiency upon Blood-Pressure—Vasodilator Effects of Epinephrin—Differential Effects of Epinephrin in Various Organs—Effects on the Circulation of the Limb—Effects on the Circulation of the Liver—Effects on the Circulation of the Spleen—Effects on the Circulation of the Kidney—Effects on the Circulation of the Intestine—Effects on the Circulation of the Brain—Effects of Epinephrin on the Heart—Effects of Epinephrin upon Pulmonary Circulation—Effects of Epinephrin upon Venous Pressure—Factors Modifying the Pressor Response to Epinephrin—Conclusion.

Relation of the Suprarenal Glands to the Circulation

R. G. HOSKINS

COLUMBUS

That the suprarenal glands play an important rôle in the maintenance of circulatory efficiency is demonstrated by the cardiovascular asthenia that results from destruction of these organs. Low blood-pressure and feeble heart action are characteristic both of Addison's disease and of the syndrome of acute suprarenal deficiency. Whether the influence of the suprarenals on the cardiovascular system is mediated directly or indirectly has not yet been satisfactorily determined. Neither has it been shown conclusively which component of the suprarenal, the cortex or the medulla, has most to do with the maintenance of circulatory vigor. The trend of modern work is toward a conclusion that the cortex is the more significant. That there subsists, however, between the suprarenal medulla and the circulatory mechanism, at least a *pharmacological* relationship, is unquestioned. The evidence regarding the effect of epinephrin, the active principle of the medulla, upon the heart and blood-vessels is discussed in succeeding paragraphs.

The crux of the problem is whether or not under ordinary conditions epinephrin is discharged from the suprarenals into the blood-stream in sufficient amount to exert a significant influence upon the physiological process. This problem is discussed at length by Professor Stewart in another chapter.

Earlier Work on Suprarenal Pharmacology

Oliver and Schäfer were the first to make systematic studies of the effects of suprarenal extracts upon the circulation. Their work was reported in preliminary form before the British Physiological Society in March, 1894, and March, 1895. Their observations were published in full in the latter year. It is true that several earlier investigators had worked with suprarenal extracts, but they had made only gross studies of such functions as respiration, temperature, and general behavior as in-

fluenced by toxic doses. None of these studies cast any significant light upon the physiology of the gland.

Oliver and Schäfer used several sorts of extracts—aqueous, alcoholic, and glycerin. Sometimes the fresh tissue was extracted, but often it was desiccated and thus preserved, the extracts being made up from the dried material as needed. The suprarenal material was derived mainly from calves, but some also from sheep, guinea-pigs, cats, dogs, and man. The effects in general were similar with all types of preparations, with the exception of the fact that dry alcohol or dry ether failed to extract any active substance from perfectly dry tissue.

The experiments were carried out mostly on dogs, but cats, rabbits, guinea-pigs, and one monkey were also used. Generally, chloroform-morphin anesthesia was employed. The extracts were ordinarily administered by vein. The dosage varied somewhat but was usually less than the equivalent of 0.2 gm. of fresh gland. Maximum effects were obtained when doses of 1.5 mg. of fresh gland per kilogram of body weight were used.

Some observations were made upon the effect of subcutaneous administration. It was found in case of dogs and cats that only relatively large doses produced any effect at all. With these slight transitory disturbances of the pulse rate, the respiration and the temperature were noted. These were accompanied by more or less hebetude of a few hours' duration. Rabbits, on the other hand, frequently reacted much more strikingly. With larger doses death often resulted; smaller doses produced no evident effect.

A large part of Oliver and Schäfer's paper is devoted to a discussion of the effect of suprarenal extract upon the arterial system. In these studies four methods were used: (1) Blood-pressure was determined by means of the mercury manometer; (2) Plethysmographic studies were made of the changes in the volume of the limbs, spleen, and kidneys; (3) The arterial system of pithed frogs was perfused with saline solutions to which suprarenal extracts in various concentrations were added and the effects on the rate of outflow noted; (4) Finally, direct ocular observations of large and small blood-vessels were made.

Very striking evidence was obtained that suprarenal extracts contain some substance which has a powerful constricting effect upon the arterioles of the body. This constriction led to a remarkable rise of blood-pressure, even when accompanied, as was usually the case, by cardiac depression. In the frog perfusion preparations so great was the arteriolar contraction that the outflow was almost completely abolished. In the larger arteries of the experimental mammals "passive expansion" was noted. In the plethysmographic experiments the effects in the different organs varied. The kidneys and spleen diminish greatly in volume, although a preliminary expansion was not infrequently seen. In the limb, contraction was

more commonly observed but expansion was also frequently seen. The difference was ascribed by the authors to variations in the relative parts played by passive expansion in the larger vessels and active constriction in the smaller. In the kidneys, in some instances, towards the end of the experiments "passive dilatation" was observed. No direct plethysmographic studies were made of the reaction in the intestine, but by direct inspection well-marked generalized splanchnic vasoconstriction was evident.

Attention was directed to the problem as to how the vasoconstrictor effect was mediated. The rôle of the nervous system was first investigated. It was found that perfusion of suprarenal extracts through the vascular bed of the frog was equally effective after section of the spinal cord or of the nerves to the limbs. Hence it was concluded, and correctly, that the effect is largely, at any rate, peripheral and independent of the nervous system proper. That the effect of the extracts was upon the tissues directly was indicated to some extent also by the brief latent period intervening before the reaction was apparent.

In the experience of these investigators, the extracts invariably produced a rise of arterial pressure, "never a fall." The important observation was also made at this time that the pressor effect of a given dose of suprarenal extract was materially augmented if the vagi were cut or paralyzed by a suitable dose of atropin. Under these conditions Oliver and Schäfer witnessed rise of blood-pressure from two to five times the original height. The persistence of the effect varied more or less in accordance with the dosage. The maximum persistence seen in the dog was four minutes, and in the rabbit six minutes, following single doses. The blood-pressure curves reproduced by way of illustration of the report are mostly of the smooth, monophasic wave form, though occasionally curves with a preliminary dip, such as have since become very familiar to pharmacologists, were seen. Curiously enough, the depressor phase which is so characteristic of epinephrin curves was never secured.

The effects of suprarenal extracts upon the heart were studied both in frogs and in mammals. When the isolated frog heart was perfused the addition of suprarenal extracts led to a marked increase in the rate and, less definitely, an increase in the strength of the beat. The irregularities of force and rhythm not uncommonly seen in such isolated heart preparations, were not infrequently elicited. In case of the mammal with the vagi intact, the effect, on the other hand, was commonly a marked inhibition. This was first apparent in the auricles. It was usually preceded by a brief augmentation which rarely lasted, however, more than one or two minutes. Following the inhibition of the auricles, the ventricles then assumed a slower rate. This inhibitory effect was totally abolished by vagotomy or atropin. Instead of depression, a marked

augmentation both of rate and force was then seen. In one case fibrillation of the ventricle ensued when the blood-pressure reached a maximum height.

The British observers investigated the distribution of the active principle as between the cortex and the medulla of the suprarenals. Glands were frozen and the cortex carefully peeled off from the medulla. Extracts were then made from each portion. Those from the cortex when injected gave little or no reaction, whereas those from the medulla were very active. Opportunity was offered to investigate the activity of extracts from the glands of a patient who had died of Addison's disease. The extracts proved to be inert.

This epoch-making paper of Oliver and Schäfer's is reported somewhat at length because it embodies a large proportion of all of the more significant data that have been recorded as regards suprarenal pharmacology. A few months after the publication of this paper there appeared the reports of the Polish physiologists Cybulski and Szymonowicz, who had independently been studying the same problem in much the same way. In general, Oliver and Schäfer's observations were confirmed, but the Polish investigators were led to one erroneous conclusion, namely, that the action of suprarenal extracts is exerted primarily upon the central nervous system. Cybulski contributed an additional observation of major importance, that is, that the blood of the suprarenal vein could be shown to contain an active substance presumably the same as that in the suprarenal extracts.

All of these new data seemed to fit in most satisfactorily with those previously secured by Addison, Brown-Séquard and others, and to permit a conclusive answer to the much debated problem as to the functional significance of the suprarenal glands. The obvious deduction Oliver and Schäfer did not fail to draw. It had previously been shown that deficiency of the suprarenals leads to circulatory failure. It was now seen that the glands are capable of elaborating a substance that is astonishingly potent in stimulating the heart and augmenting vasomotor tonus. This substance—or at least one having similar properties—can be found in the efferent blood from the glands. The conclusion seemed unavoidable that the function of the suprarenals is to secrete an active substance which exerts a constant stimulating influence on the cardiovascular mechanism, and thus maintains blood-pressure. Thus the "tonus theory" was formulated. It immediately received unquestioned acceptance and stood almost unchallenged for two decades. Indeed, it still serves as a cardinal doctrine in the minds of one class of endocrin theorists, despite the fact that numerous data are now on record with which the tonus theory can scarcely be reconciled.

During the next few years after the publication of this epochal paper on suprarenal pharmacology, the observations were extended in various

ways but nothing further of fundamental significance was added. The isolation of epinephrin permitted more satisfactory quantitative studies. It was found that the threshold dosage for pressor effects from intravenous injections is as low as 0.0005 mg. and that doses of the magnitude of 0.001 mg. per kilo. never fail in a normal test animal to give clean-cut pressor reaction of such magnitude, for example, as 25 mm. of mercury. With larger doses pressures of 250 to 300 mm. were found to be easily obtained and such as are not elicitable by any other known means (Biedl). As Oliver and Schäfer pointed out, the effects of even maximal single doses are brief, but Biedl reported that he was able to maintain for hours a pressure of 140 to 160 mm. by constant infusion of epinephrin in mammals, even after total destruction of the central nervous system. Maximal effects are obtainable with such doses as 0.1 mg. Further augmentation of the quantity injected, it was found, is likely to lead to immediate disastrous effects, such as ventricular fibrillation or pulmonary edema.

That the pressor effect of epinephrin is due to its action partly on the heart and partly on the peripheral blood-vessels was recognized by the earlier investigators. While cardiac depression may result from vagus stimulation incident to the high blood-pressure following the administration of large doses of epinephrin, it is not to be supposed that the sustaining influence of the drug upon the heart is in abeyance. Without this influence, a given elevation of arterial pressure would result in materially greater cardiac depression.

The vaso-constrictor effect of epinephrin can be recognized by inspection of the tissue upon which it acts. Blanching the conjunctiva or nasal mucosa by use of this substance is a well-known clinical procedure. A small quantity of dilute solution introduced intracutaneously results in an area of alabaster whiteness. Cybulski and Szymonowicz, as previously mentioned, believed that the vasoconstriction is due to the action of the drug on the medulla oblongata. Oliver and Schäfer's report, however, that the effect is readily elicited after destruction of the nervous system was early and abundantly confirmed. Indeed, if the animal remains alive following the denervation of a given organ, the irritability of the tissues to epinephrin becomes materially augmented. That the vasomotor effect is exerted largely on the arterioles was deduced from the fact that the large arteries may even enlarge during the time the blood-pressure is at its height. This expansion of the arteries is due, however, to relative rather than absolute lack of response to injected epinephrin. This can readily be shown by exposing rings of isolated artery to the action of the drug. Some degree of contraction is noted in almost every case. While the greater part of the pressor effect is due to direct cardiovascular stimulation, it is probable that the vasoconstrictor centers are also stimulated to a minor extent. Biedl found that the introduction of epinephrin into the carotid artery resulted in the immediate increase of blood-pres-

sure. Whether the result is due to a true stimulation of the medulla by the drug itself is doubtful, however. The pressor effect is quite plausibly to be ascribed to the partial anemia produced in the center. That the irritability of this center is augmented by interference with its local circulation is easily demonstrated by such methods as ligation of the carotid arteries. To what extent the pressor reaction to epinephrin may be dependent upon stimulation of the sympathetic ganglia seems not to have been satisfactorily determined beyond the fact that it is slight. Hartman has found that vasodilator effects, at any rate, may be obtained by applying epinephrin directly to sympathetic ganglia.

Locus of Stimulation by Epinephrin

As brought out in the preceding chapter, the action of epinephrin is confined exclusively to tissues innervated by the sympathetic nervous system proper (the thoracico-lumbar autonomic fibers of Langley). The precise site of the stimulation has been much discussed. The essential features of the pertinent evidence may be summarized. Of primary interest is the fact that section and subsequent degeneration of the sympathetic fibers do not abolish the epinephrin reaction, hence the central nervous system and the ganglia play at most a minor rôle. On such evidence as this Langley postulated that the effect of the drug is on the smooth muscle directly. Later, Brodie and Dixon studied the matter in more detail. It was discovered that apocodein, an alkaloid obtainable by dehydration of codein, has the property when given in large doses of blocking sympathetic fibers. Thus it causes vasodilatation with resultant hypotension. Following the administration of apocodein, epinephrin fails to give a reaction. The application of barium chlorid or other direct cell stimulant, however, shows that the smooth muscle itself is still irritable. From these data it follows that the point of stimulation lies between the sympathetic nerve terminals proper and the muscle cells. The hypothetical element thus intervening in the myoneural junction has been called by Langley the "receptive substance." It would seem to correspond in function to the percussion cap of a loaded cartridge. Regarding the morphological nature of this myoneural junction, very little is known.

As to how epinephrin produces its effects, little beyond speculation can be offered. It acts with astonishing promptness when applied to such a sensitive tissue as a segment of rabbit intestine. When administered intravenously, the latency of the reaction is not appreciably greater than the time required for transportation of the drug to the reacting tissue. Whether the epinephrin enters into chemical combination with the reacting tissue in the sense of becoming incorporated in the myo-

neural junction substance is not clear. It is quite possible that Straub's principle as regards the action of drugs holds here,—namely, that a given substance may exert its influence merely by the process of penetrating the effector cells. That is, it is inactive either when prevented from passing into the cell or after its passage. Favoring this supposition is the fact that it is not possible by a single dose of epinephrin administered intravenously to produce more than a very brief reaction. If the action of the drug is due, however, merely to its transit into the cell, we must assume that epinephrin is destroyed in the myoneural receptive substance. This follows from the fact that it is possible by continuous infusion to maintain elevated blood-pressure for hours. If the drug were not being continuously destroyed, equilibrium would be quickly established within and without and passage of the drug then cease.

Destruction of Epinephrin in the Body

Such considerations as the foregoing raise the question, How is epinephrin destroyed in the body? No very satisfactory answer can be offered. That it is not excreted as such is generally believed. It is not found in the urine except in traces after the administration of large doses. It has not been recognized in any of the other excretory fluids in man, though it has been found in the dermal secretion of a West Indian toad (Abel).

The fact that epinephrin is readily oxidized suggests that it is by this means that destruction of the substance occurs. But against this conception several objections may be raised. If mere oxidation were the method involved, passage through the lungs, with exposure there to maximal oxygen tension, should lead to partial or complete destruction. As a matter of fact, epinephrin can be passed through the pulmonary capillaries with little or no reduction of its concentration in the blood. Epinephrin, when added to aerated, defibrinated blood kept at body temperature, persists with relatively little diminution for hours. It is this fact that renders possible comparative assaying of epinephrin in the blood. Furthermore, it appears fairly clear that epinephrin, as a matter of fact, is destroyed in the tissues that have a reducing rather than an oxidizing tendency. Also, epinephrin is much more unstable in alkaline than in acid solutions. Active tissues are constantly producing acid metabolites; hence epinephrin would supposedly meet augmented acidity upon its passage from the peripheral capillaries. Kretschmer has reported that he was able to prolong the hypertensive reaction to epinephrin very materially by intravenous administration of acid. This result, however, the writer was quite unable to corroborate by the use of acid in any quantity even remotely approaching the maximal amount that could be formed in the normal liv-

ing body. As a matter of fact, the buffer properties of the blood would seem to vitiate any such experiment as Kretschmer reported.

Oliver and Schäfer believed that epinephrin injected into the blood stream is removed by the tissues—especially muscle—stored, and subsequently oxidized. That such is the case has not been demonstrated. Langlois reported that epinephrin was rapidly rendered inert when added to freshly pounded liver or intestinal tissue. Livon obtained similar results with liver and skeletal muscle. Other observers, however, have failed to corroborate these findings and have reported destruction of epinephrin under such conditions takes place only when concentration grossly transcending physiological limits are employed. For a time much stress was laid on the fact that fresh pancreas pulp rapidly causes the destruction of epinephrin. Largely upon this fact an elaborate theory of pancreas-suprarenal antagonism was founded. The destruction of the epinephrin by pancreatic material seems definitely to be ascribed to its alkalinity.

Sajous(*c*) has brought together numerous observations which have led him to infer that epinephrin is joined to hemoglobin and serves to catalyze respiratory activity, but no proof has been offered that such is the case, beyond the fact that venous blood is oxidized somewhat more rapidly in the presence than in the absence of epinephrin. The fact that epinephrin augments the affinity of hemoglobin for oxygen would seem to indicate that it would thereby impede the more important respiratory process, namely, the discharge of oxygen from the hemoglobin to the tissues.

That epinephrin introduced into the blood-stream is destroyed by the particular tissues in which reactions occur is widely believed. Battelli noted a disappearance of epinephrin when perfused through the liver. Other observers, however, have failed to corroborate this. Langlois found that a given quantity of epinephrin, which, when injected into the jugular vein produced a marked systemic reaction, was without effect if introduced into a mesenteric vein. Carnot and Josserand found that if epinephrin was injected into a carotid or femoral artery and thus sent through the capillary bed, little systemic reaction followed; that is, only such as would result from the local action. Circulation of the drug through the capillaries supplied by the mesenteric artery was even more effective in reducing the pharmacodynamic activity. These latter observations were confirmed by Elliott, who proposed the view that epinephrin disappears from the blood at a rate directly proportional to the local reaction produced. It is to be kept in mind, however, that larger doses of epinephrin thus administered by artery cause a marked vasoconstriction and hence partial or almost complete occlusion of the local blood-stream. It is possible, therefore, that the assumed "disappearance" means merely a holding back of the epinephrin and feeding it into the blood-stream at so slow a rate as to prevent its detection.

That epinephrin persists in the blood-stream for a considerable period

after its gross pharmacodynamic effects have disappeared, seems sufficiently demonstrated. Weiss and Harris have reported an investigation which has been frequently referred to in this connection. In the frog one iliac artery was ligated and epinephrin was injected into the general circulation. Comparative studies were made in the blood-vessels of the webs of both feet. After the vasoconstrictor effect in the non-ligated limb had entirely disappeared the ligature was removed from the artery and the blood allowed to pass to the other web. An intense vasoconstriction now appeared in the previously ligated side. It has also been reported that blood removed from an animal immediately after the perceptible effect of a large dose of epinephrin has disappeared will cause a rise in pressure if injected into a second animal. More recently, Auer and Meltzer(*a*) have shown that when epinephrin is administered hypodermatically in the denervated ear of a rabbit, a well-marked local vasomotor reaction promptly appears and persists for hours.

From the data at present available no satisfactory conclusion can be reached as to how epinephrin is normally disposed of. Indeed, the theory is not excluded that the suprarenal glands themselves remove epinephrin from the blood-stream when, after special stimulation, it appears there in any appreciable concentration; similarly, that the precursors of epinephrin are taken up and metabolized to some inert form, which is then excreted in low concentration by way of the circulation as urea is removed from the liver.

Effect of Acute Suprarenal Deficiency upon Blood-Pressure

Oliver and Schäfer's "tonus theory" postulated that blood-pressure is kept up to normal height by a constant discharge of minimal quantities of epinephrin into the blood-stream, and resulting stimulation of the cardiovascular apparatus. If this were the case, it should follow, in view of the evanescent reaction to injected epinephrin, that ligation of the suprarenal veins would lead to a prompt fall of pressure.

Strehl and Weiss put the matter to experimental test. Their experiments were made upon rabbits. One suprarenal was first removed. The vein leading from the intact gland was then occluded for a brief period while arterial blood-pressure was being recorded. Characteristically, blood-pressure at once was lowered as much as 10 to 25 mm. of mercury. Upon release of the vein the pressure again returned to, or above, the normal height. In some cases the glands were removed in toto. The results, however, were not uniform. In certain animals no fall of pressure occurred. The experiments were of very brief duration, the glands being occluded for only a few seconds to two or three minutes. The graphs

that are published in illustration of the article as compared with those that the writer has obtained suggest that either the vena cava itself might have been materially occluded in the process of shutting off the suprarenal circulation, or that the ligature included a considerable number of splanchnic fibers, thus leading to a sharp fall of arterial pressure.

Young and Lehman repeated these occlusion experiments, using dogs as subjects. The ligatures in their investigations were kept in place for periods of ten to thirty minutes. Very little fall of blood-pressure was observed and any such occurred very gradually. Upon releasing the ligatures in three of their eight experiments a decided rise of pressure occurred; in two a slight rise; and in three no change. Young, in a repetition of the experiment, observed no significant fall of pressure for hours after tying off the glands.

In a discussion of the work of Strehl and Weiss, Kahn (1909) pointed out that they had failed to recognize an important source of error in their experiments. The mere irritation of the peritoneum, such as was involved in the manipulations incident to ligating the veins from the suprarenal, is capable of evoking depressor reflexes with resultant reactions quite as extensive as those figures by Strehl and Weiss. In Kahn's paper a tracing is reproduced which shows a clean-cut fall of blood-pressure following ligation of the suprarenal vein in an animal from which both suprarenals had previously been extirpated. In only one instance in many experiments did this investigator see a fall of pressure that could properly be ascribed to occlusion of the venous outflow from the suprarenal gland.

Biedl reported that after removal of the suprarenals from an extraperitoneal situation to which they had been transposed, there was a fall of blood-pressure lasting fifteen to thirty minutes, but at the end of that time the blood-pressure gradually increased and by the next day had regained a normal level. In animals in which particular care was taken to avoid too profound anesthesia and operative severity, blood-pressure usually was normal for two or three days after suprarenal extirpation.

In 1912 the problem was again investigated by Hoskins and McClure. Eleven dogs served as subjects. The effects of anesthetics upon gland discharge being unknown, a variety of substances was used: urethane, urethane and ether, ether alone, and chloroform. The method of procedure in 9 cases was essentially that of Strehl and Weiss. After inserting a cannula in the carotid artery the abdomen was opened by a median incision and, while the viscera were protected by warm towels, the ends of strong ligatures were inserted through the body-wall in such a manner that, by subsequent traction, the circulation of each suprarenal could be cut off. The abdomen was then closed. After waiting for some time for the immediate effects of the operation to pass off, recording of arterial pressure was begun. After blood-pressure had been maintained for some minutes at a constant level, one ligature was drawn tight then, after a

three to five minutes' interval, the second also. Post-mortem examinations showed that the ligatures in each case had successfully occluded the lumbo-adrenal vessels. In two instances the suprarenals were dissected free and tied off by mass ligatures directly while blood-pressure was being recorded.

In view of the evanescent nature of circulating epinephrin, the experiments were continued only from ten to thirty minutes. It was assumed that any direct results of suprarenal deficiency would occur within that time. The results agreed consistently with those of Young and Lehman. In only one case, after ligating off a gland, was any significant fall of pressure observed. Usually, at the moment of tying the ligature there was a brief fluctuation of pressure, sometimes upward and sometimes downward, but the original level was quickly regained.

More recently Austmann, Halliday, and Vincent have also subjected the problem to renewed study. They offered the criticism that the time allowed in previous experiments was not sufficiently long to be completely convincing. In their series dogs were employed. The suprarenals were extirpated or their blood-vessels ligated, and continuous records were kept of the blood-pressure under simple ether anesthesia during periods of from 12 to 40 hours. From control animals curves were similarly obtained under ether anesthesia but with the suprarenals intact. With a few individual exceptions, the curves were very similar in the two series. The animals deprived of their suprarenal secretion lived as long as the controls and the blood-pressure showed no greater tendency toward a fall.

Bazett (1920) has again repeated the extirpation experiments on cats and rabbits and has confirmed the results of earlier investigators to the effect that the operation fails to produce any such prompt fall of blood-pressure as the "tonus theory" demands.

It is obvious, therefore, that under the conditions of these experiments, at any rate, the suprarenal glands do not discharge epinephrin in sufficient quantity to have any significant direct effect upon blood-pressure.

Vasodilator Effects of Epinephrin

The first definite evidence that suprarenal extract may produce a fall in blood-pressure was reported by Moore and Purinton in 1900. These observers set out to determine the threshhold doses of such extracts. Suprarenal glands of cattle and sheep were split and the medullary portion mechanically separated from the cortex. Aqueous extracts were then made of the material, the protein components being largely removed by boiling in a slightly acid medium. Dilutions of 1:100 to 1:1000 were employed. It was assumed that in such high dilutions the effect of any "foreign substances" that might be present in the concentrated extract would be re-

duced to negligible proportions. The experiments were carried out on 7 dogs under chloroform anesthesia. The vagi were paralyzed by means of atropin. Carotid blood-pressure was recorded. From ten to twenty injections were made in each animal. It was found that the intravenous injection of extract of the medullary portion of the glands in doses equivalent to 0.005–0.010 mg. of the gland substance per kilogram body-weight gave pure rises of pressure of from 20 to 40 millimeters. With doses of 0.001 to 0.003 mg., a brief rise followed by a well-marked fall of pressure was seen. In still smaller doses only depressor effects were obtained. Such depressor effects were not elicited, however, in all cases; two of the seven animals gave only pressor responses. These investigators left open the question whether the reversal of reaction was due to the presence of some unrecognized "impurity" better able than the true "active principle" to maintain its potency in high dilution or to the stimulation of some true depressor mechanism.

The fact that suprarenal extracts are able to produce vasodilatation and thus fall of blood-pressure was reported by Dale (1906). In the course of a study of the pharmacology of ergot he made the interesting discovery that ergotoxin or chrysotoxin has the peculiar property of paralyzing all of those sympathetic fibers which have a stimulating function, leaving more or less intact those which have an inhibitory function. A dose of epinephrin, which in a normal animal would evoke a marked rise of blood pressure, was found, after poisoning with ergotoxin, to bring about a marked fall of pressure. This work was generally accepted as proving that epinephrin can cause vasodilatation.

Somewhat before this time, however, it had been shown by S. J. and Clara Meltzer (1903) that subcutaneous injection of suprarenal extract in the rabbit can lead to well-marked and persistent dilatation of the blood-vessels of the denervated ear.

Elliott, in his classical paper in 1905, reported that he had in some cases observed very dilute solutions of epinephrin to cause lowering of the blood-pressure in the cat, but apparently he was unwilling to accept the observations as valid because he found that solutions of 1:600,000 or 1:200,000, if "slowly and exactly made," produce only rise of pressure. "Straightforward experiments failed to prove vascular dilatation by adrenalin." In 1912, however, the same investigator noted that in some cases, when the splanchnic nerves were stimulated, a drop in blood-pressure occurred, which coincided with signs of epinephrin discharge (dilatation of the pupil). He also noted that after extirpation of the suprarenals this depresor effect could be simulated by injecting epinephrin during splanchnic stimulation.

Despite such observations as the foregoing, so firmly established was the idea that epinephrin is a pressor drug that its vasodilator properties were for years deemed negligible. In connection with other investiga-

tions, Hoskins and McClure, in 1912, reinvestigated the matter. Dogs were used as experimental animals. Systematic study showed that if epinephrin is injected by vein at a slow but gradually increasing rate, at first no effect at all is apparent. As the dosage is increased the first effect to appear is depression. This may or may not be preceded by a brief inconsequential rise of pressure. In one instance a record was obtained, showing a pure hypotensive effect which persisted for several minutes, the blood-pressure promptly returning to normal when the injection was discontinued. With still larger doses it was found that a pressor effect appeared, which might exactly cancel the depressor effect, leaving the pressure, after a slight initial fluctuation, at a normal level.

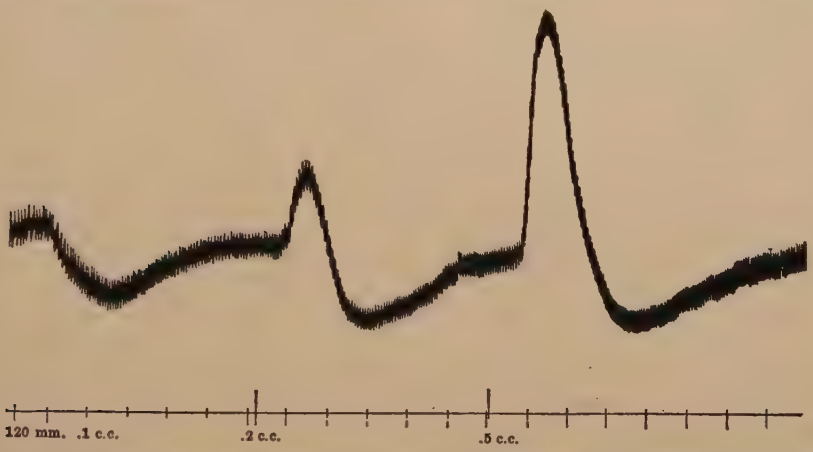

Fig. 1. Graph showing transition from pure depressor to predominantly pressor reaction in cat from intravenous injections of epinephrin. Doses, 0.1, 0.2, and 0.5 c.c. 1:10,000 solution. Time, half minutes. (After Cannon and Lyman, Am. J. Physiol.)

Still larger doses brought about the well-known pressor reaction. In one typical instance in which the point was specifically under investigation, although the characteristic depressor reaction appeared with the injection of 3 c.c. of 1:1,000,000 solution of epinephrin per minute, it was not until a dose of 17 c.c. per minute was used that a minimal sustained rise occurred. Since pure isolated epinephrin was used in these experiments, the only apparent explanation of the depressor effect was that some vasodilator mechanism had been brought into play.

In 1913 Cannon and Lyman subjected the problem to elaborate study. Cats were used as experimental animals. Epinephrin was injected by jugular vein and the dosage was accurately controlled, as was also the speed of injection, both of which are important factors in the type of reaction elicited. Blood-pressure was recorded from the femoral or carotid artery. It was found that by varying the doses all degrees of reaction from a fall of 22 per cent to a rise of almost any desired magnitude could be obtained (Figs. 1 and 2). The depression was not accompanied by

any noteworthy change in the pulse-rate or pulse-pressure, hence was ascribed to primary vasodilatation. By properly graduating the dosage, it was found possible to elicit additive depressor effects by successive doses and by increasing these to a critical point to shift the reaction to the pressor side and to obtain additive pressor effects. Pithing the brain and upper cord caused a fall in the blood-pressure level; at this lower level doses of epinephrin which previously had given depressor effects now caused only increase of pressure. There was no detectable alteration in heart action which could account for the reversal, hence it was inferred that pithing had converted the vasodilator to a vasoconstrictor response. Sim-

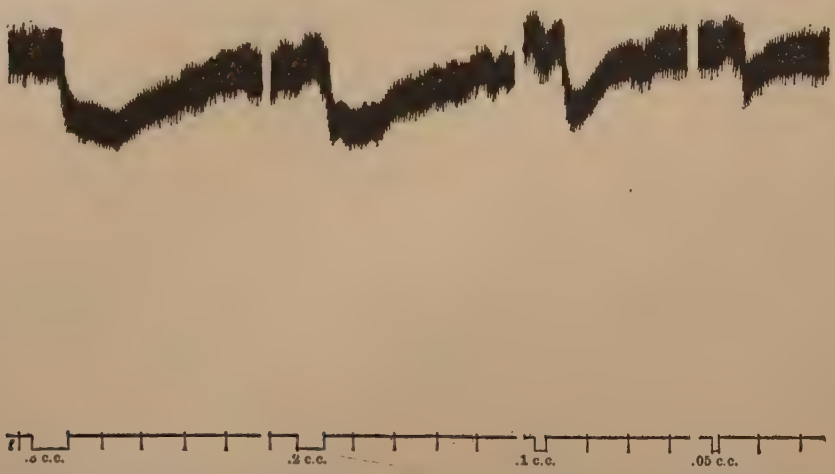

Fig. 2. Graph showing graduated depressor reactions due to varying doses of epinephrin in cats. Intravenous injections 1:100,000 solution (0.3, 0.2, 0.1 and 0.05 c.c.) given at the rate of 0.01 c.c. per second. Time, half-minutes. (After Cannon & Lyman, Am. J. Physiol.)

ilarly, the reverse of reaction could be obtained by lowering the blood-pressure either through stimulation of the depressor nerve or injection of nitroglycerin. From a consideration of all of the available evidence, the conclusion was reached that epinephrin vasodepression is not of central origin, is not due to blocking of vasconstrictor impulses, nor to stimulation of supposed vasodilator sympathetic nerve endings. The differential effects were tentatively ascribed to varying reactions of the smooth muscle according to its relative state of tonus. It is tempting, in this connection, to apply Verworn's theory of inhibition, namely, that it is due merely to subminimal stimulation qualitatively similar to that producing activity.

Hartman in 1915 again studied the depressor effects of epinephrin. Of 49 normal cats only 1 failed to give a fall in pressure following the administration of a small standard dose of epinephrin. In one interesting experiment the standard dose of epinephrin gave a fall in pressure from an initial level of 102 mm. After hemorrhage, which reduced the

level to 65 mm., the reaction was converted to the pressor type. Defibrinated blood was then injected and, as the pressure gradually rose, the depressor epinephrin reaction reappeared.

Hartman and his collaborators have more recently published extensive observations upon the epinephrin vasodilator mechanisms. They noted that if the splanchnic nerves were cut epinephrin, which had previously caused vasoconstriction, now caused only dilatation. This observation led to a study of the part played by the central nervous system. Their experiments were made upon dogs and cats, the volume changes in the intestine and in normal or denervated limbs being recorded along with systemic blood-pressure. Simultaneous records were made of the volume changes in the two hind-limbs after one had been denervated. Gruber's observation to the effect that small doses of epinephrin usually gave dilatation in the normal limb and constriction of the denervated structure was confirmed. Large doses, however, such as those which usually produce a rise in blood-pressure, caused constriction in both limbs. This was true in ten of fifteen cats. The dilatation in the denervated limb appeared to be passive since it occurred at the same time blood-pressure began to rise and persisted an equal length of time. Such dilatation was cut short or obviated with large doses of epinephrin. Dilatation in the normal limb came later than in the denervated and lasted as long as the blood-pressure was below normal.

It might be assumed that the failure to evoke dilatation in the denervated limb was due to extreme relaxation of the blood-vessels incident to loss of tonic impulses. By the use of a substance obtained from ox pituitaries, however, it was shown that such was not the case, marked dilatation occurring in both normal and denervated limbs.

The foregoing observations indicated that the central nervous system plays a considerable part in the vasodilator reaction to epinephrin. This was further shown in another way. A segment of intestine or a limb was cut off from the body circulation and independently perfused with warm oxygenated Ringer's solution. The part was left in connection with the central nervous system through its normal nerve paths. The organ was then placed in a plethysmograph and volume changes noted, or the outflow was measured directly. Injections of epinephrin were then made into the body circulation, proper, and the effects upon the organ in question noted. It was found that clean-cut vasodilator effects could readily be elicited. Since the only connection between the perfused organ and the remainder of the body was by way of the nerve paths, the vasodilatation must have been mediated by the central nervous system or the sympathetic ganglia (Fig. 3).

That the nervous mechanism involved in this reaction was below the cerebrum was proved by the fact that the destruction of this organ failed to abolish the reaction; likewise it failed to prevent the fall in blood-

pressure which charcteristically results from suitable doses of epinephrin. When, however, the medulla was destroyed, this depressor reaction was converted to pressor. But in spite of this reversal the dilator mechanism in both the limb and the intestine was found to be functional. Destroying the spinal cord at successive levels failed to abolish the dilator response, and Hartman concluded that, contrary to his previous belief, the mechanism through which the dilatation was mediated lay outside the central nervous system proper.

By exclusion, then, it would appear that the mechanism is located in the sympathetic ganglia. Direct experimentation indicated that such is the case. In 6 dogs the intestine was independently perfused. Epi-

Fig. 3. Graph showing the arterial pressure reaction and leg volume expansion in a dog following the injection of 0.5 c.c. 1:10.000 epinephrin by jugular vein. The leg was perfused with oxygenated Ringer's solution and isolated from the body circulation. The nervous connections were intact. (Reduced one-half.) (After Hartman and Fraser, Am. J. Physiol.)

nephrin injected by jugular vein caused dilatation. When, however, the splanchnic fibers peripheral to the ganglia were sectioned the dilator reaction was abolished. Similarly, it was abolished by painting the ganglia with nicotin, thereby blocking the connection between the preganglionic and postganglionic neurons.

The location of the vasodilator mechanism for the hind-limbs was then determined. Since, as earlier shown, it is not in the spinal cord, it must be in either the ganglia of the sympathetic chain or of the dorsal roots. The hind-limb of a dog was placed in a plethysmograph. The last five lumbar and the first sacral sympathetic ganglia were destroyed on the corresponding side. The limb was then completely isolated from the body circulation and perfused. Injection of epinephrin into the jugular vein evoked marked dilatation. Similar results were obtained in other animals, though not uniformly. In some cases destruction of the sympathetic ganglia left the dilator mechanism functioning, but destruction of the dorsal root ganglia abolished it. It appeared then that the dilator mechanism for the limb may be located in either the dorsal root ganglia

or the sympathetic ganglia. In subsequent experiments it was found possible to bring about dilatation in the limb by the application of epinephrin directly to these ganglia.

A systematic study was also made of the vasodilator reactions in the various orders of vertebrates. The mechanism was found to be absent in reptiles, birds, and one order of mammals, the rodents (rats and rabbits). Its presence was demonstrated, however, in one the lower mammals, the opossum. It was found present in all of the carnivors examined (cat, dog, ferret). In the cat it appeared, however, the mechanism was not functional until about the eleventh week of life.

That vasodilatation is a characteristic and, perhaps, the most significant phase of the vasomotor reaction to epinephrin can no longer be questioned. It seems evident that the injection of any effective quantity stimulates primarily the vasodilator mechanisms. Whether fall of blood-pressure results depends upon the extent to which vasoconstrictor mechanisms are also brought into play. A considerable amount of direct evidence supports the inference that the dilator mechanisms have a lower threshold for epinephrin than have the constrictor. Even in organs which give well marked vasodilator responses with smaller dosages, constriction appears when the dosage is sufficiently increased. This apparently is always true in case of the isolated organs. When, however, the drug is administered to the intact animal, the vasoconstrictor tendency in organs having the less effective vasomotor mechanisms may be overcome by high systemic blood-pressure and relative vasodilatation produced.

The term "vasodilator mechanism" as herein employed can as yet be given no very definite meaning. Whether the "mechanism" is one which involves direct final effects or whether it merely inhibits vasoconstrictor mechanisms remains to be determined. In the absence of adequate data on the general physiology of vasodilatation, no convincing inferences can be offered.

The most that can be definitely said at the present time is that epinephrin is neither a vasoconstrictor nor a vasodilator substance, generally speaking, but is either, depending upon the dosage employed, the organ involved and the condition of the organism as a whole. Further data bearing upon the point will be found in succeeding paragraphs.

Differential Effects of Epinephrin in Various Organs

In a consideration of the effects of epinephrin upon the circulation, attention is directed primarily to the reactions in the heart and in the peripheral blood-vessels. Of subsidiary but potentially considerable importance are the effects upon pulmonary circulation and upon venous blood-pressure. Any material fall in the venous pressure or any consider-

able block in the pulmonary blood-stream may interfere with the adequate filling of the left side of the heart and hence cause diminution of systemic blood-pressure.

Earlier researches having definitely shown that epinephrin is capable of evoking either vasodilator or vasoconstrictor effects, it became important to determine how and to what extent these effects are associated in a composite reaction to the drug. Hartman, in 1915, subjected the problem to direct study.

His experiments were made upon cats. Urethane, was the anesthetic used throughout. The epinephrin was administered by jugular vein in concentration of 1:100,000. In most cases injections of 0.2 c.c. were made at a uniform rate in each instance over a period of from fifteen to thirty seconds. Blood-pressure was registered from the carotid artery.

In the first series of experiments the circulation was confined to the extra-splanchnic vessels. This was brought about by ligating the inferior and superior mesentery arteries, the celiac axis, and sometimes also the renal arteries. Of 23 animals thus prepared, 14 showed a distinct fall of arterial pressure after injection of the standard dose of epinephrin. In 4 animals in which there had been a preliminary rise of pressure followed by a fall, the same dose failed to cause a rise after the splanchnic vessels had been occluded. In two instances in which, previous to the ligation of the splanchnic vessels, a rise of pressure alone was obtained, after the ligation, only a fall was produced. In another instance, a depressor effect of 14 per cent was increased to 32 per cent by occlusion of the splanchnic vessels. From these experiments Hartman drew the correct conclusion that small doses of epinephrin bring about relaxation of the "peripheral arteries." In no case was evidence of constriction observed. No attempt was made in this study to differentiate the effects in the various "peripheral" structures involved.

In a second series of observations the circulation was confined to a considerable extent to the splanchnic area. Ligatures were placed about the abdominal aorta above the iliac arteries, about both subclavians and both carotids. Thus, in addition to the splanchnic circulation, there remained that of the trunk and the thoracic viscera. Observations were carried out on 20 animals, using the same standard dose of epinephrin, administered in the same way as in the preceding series. In all but 2 of the 20 cases this standard dose caused only a rise of arterial pressure, an effect just the opposite of that caused by the same dosage before the vessels were occluded. An exception to this general statement is that immediately after the occlusion, while the blood-pressure was abnormally high, depressor effects were sometimes seen, but later, as the pressure decreased, the fall was converted to a rise. As the pressure decreased below normal the percentage rise from the standard dose usually increased.

In 4 animals the two types of experiment were combined, both splanch-

nic and peripheral responses being obtained after occluding first one group of arteries and then releasing these and occluding the second group. In each instance clamping the extra-splanchnic arteries caused the vascular response to the standard dose of epinephrin to change from the normal fall to a rise of pressure (Fig. 4). Clamping the splanchnic vessels, on the other hand, in all except one case, permitted the eliciting of depressor effects only.

Effects on the Circulation of the Limb.—The first studies of the effects of epinephrin on the limb volumes were reported in Oliver and Schäfer's paper previously discussed. Contraction usually was observed, though occasionally expansion of the limb occurred. These results were

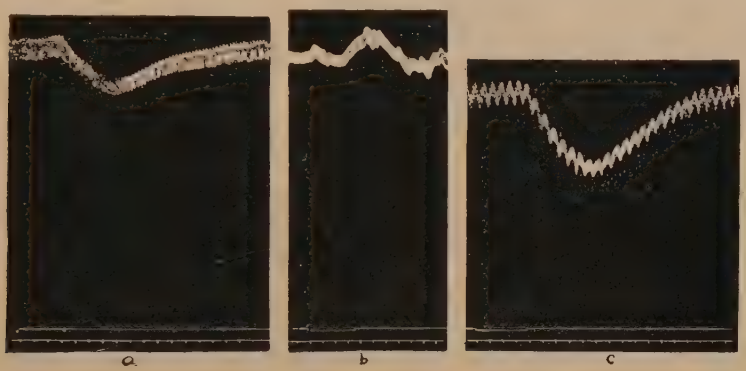

Fig. 4. Differential effects of epinephrin, 0.2 c.c. 1:100,000 solution by vein, upon blood pressure, when the whole circulation, the splanchnic area, and the limbs respectively were chiefly involved. In *a* normal conditions maintained; *b*, the peripheral vessels were clamped; *c*, splanchnic arteries clamped. Time, 5 seconds. (After Hartman, Am. J. Physiol.)

confirmed by Vincent, who added the observation that expansion was particularly likely to occur toward the end of the experiment. This expansion was regarded as "passive." In certain instances one limb expanded while its fellow contracted. This inconsistency was ascribed to a struggle between active constriction of the arterioles and dilatation of the larger vessels within the plethysmograph.

A considerable number of studies have been made regarding the effects of epinephrin on the outflow from perfused limbs. In the use of the Läwen-Trendelenburg perfusion method of assaying epinephrin abundant proof has been secured that this substance in all dilutions ordinarily causes vasoconstriction in the legs of the frog. Gerhardt attempted to study directly under the microscope the effects of epinephrin on the blood-vessels of living muscle. He was unable to detect changes in the caliber of either the arterioles or the venules, but inferred that the arterioles must have constricted since otherwise the veins would have shown dilatation as the result of increased arterial pressure that ensued.

The foregoing observations had been interpreted as indicating that epinephrin causes vasoconstriction in skeletal muscle, but the effect of the drug on the cutaneous vessels in such experiments had not received adequate consideration. That it causes vasoconstriction in the skin had been reported by Velich, Baum, Elliott, and Vincent. From the study of the limb as a whole, therefore, without taking into account the extent to which the skin participates in the reaction, no conclusion is justified regarding the effects in the muscle.

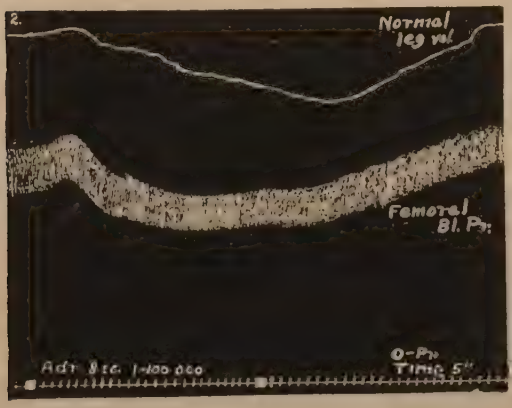

Fig. 5. Graph showing contraction of the normal leg of a dog as result of infusion of a depressor dose of epinephrin by vein. (Reduced to one-half.) (After Hoskins, Gunning, and Berry, Am. J. Physiol.)

The differential effects in both skin and muscle were studied by Hoskins, Gunning, and Berry (1916). Dogs were used as the experimental animals. These were anesthetized by ether or ether and morphin. The plethysmograph used for the leg was of the familiar Mosso type, consisting simply of a glass cylinder of appropriate diameter, adapted to the leg by means of a thin rubber cuff. Injections or infusions of epinephrin were made into a femoral vein. Arterial blood-pressure was recorded simultaneously with the changes of limb volume.

The effects of epinephrin on the volume of the intact limb were first investigated. Varying dosages were used, from those which gave a fall of systemic pressure to those causing a sharp rise. In most cases the volume of the limb was decreased, irrespective of the systemic reaction. (Fig. 5.) In a few instances, however, increased volume was noted. One such case is shown in Fig. 6. The expansion noted by previous observers in such cases had been regarded as merely passive. In this case it is to be noted that the limb did not begin to increase in volume until the general pressor reaction had passed and it continued for some time after the pressure had regained essentially its normal level. The expansion was obviously due, therefore, to some other factor than elevation of systemic pressure. In all, 156 experiments were

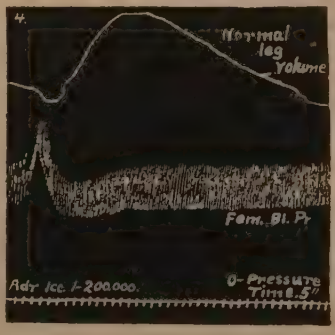

Fig. 6. Graph showing expansion of normal leg of dog under the influence of epinephrin by vein. (Reduced to one-half.) (After Hoskins, Gunning, and Berry, Am. J. Physiol.)

made in 25 different dogs. In 17, no other effect than contraction was seen at any stage of the experiment or with any dosage. One showed only expansion of the limb, while 7 showed sometimes one and sometimes the other effect, depending upon the dosage or a change in the condition of the animal during the course of the experiment.

The next step was to determine whether, and if so, to what extent, the limb contraction was due to vasoconstriction in the muscle. The components of the limb to be considered are the bone, muscle, and skin. Since the volume of the bone is fixed, the contraction must have been due to vasoconstriction in either the muscle or the skin. To determine the relative parts played by each, the volume change was first determined in the intact limb and then after removal of the skin. The result of removing the skin was striking. Under nearly all conditions of dosage, duration of administration, and resultant effects upon blood-pressure, epinephrin caused expansion of the skinned leg. If, however, very large doses were used contraction ordinarily occurred (Gunning). The experiment was varied by recording simultaneously the volume changes in two legs, one being skinned and the other intact. The former dilated while the latter ordinarily contracted. From such observations it follows that the total effect in the limb is a composite made up of dilatation in the muscle and constriction in the skin.

This deduction was put to direct test. Capps and Matthews (1913) had showed that epinephrin injections of the magnitude used in these experiments have little or no effect upon venous blood-pressure. Measuring the rate of outflow from an open vein, therefore, under various conditions of epinephrin administration should afford a reliable index of the effects of such administration upon the blood flow in an intact animal. A femoral vein was exposed in the groin. One of its branches coming from an underlying muscle was further isolated and cannulated. Similarly, a cutaneous branch of the same femoral vein was cannulated. The venous outflow was then recorded by means of a drop marker. Epinephrin was administered intravenously, either by instantaneous injections or by infusions at various rates. The rate of venous outflow from the muscle was increased, while that from the skin was decreased. The experiments were repeated many times. The effects in both cases were proved to be active because they occurred independently of increase or decrease in systemic blood-pressure.

The foregoing observations were subsequently confirmed by Hartman and Fraser and by Gruber(*c*). Gruber reported the additional observation that cutting the nerves to a muscle prevents vasodilatation in the denervated region during the early period in which local vasomotor tonus is abolished. Subsequently, however, as vasomotor tonus is regained it was found that epinephrin vasodilatation can again be evoked (Fig. 7).

In man, according to Rosenow (1918) intramuscular injections of epinephrin characteristically result in an augmented volume of the forearm.

From a teleological point of view, it is interesting that doses of epinephrin of the magnitude obtainable by stimulation of the suprarenal glands have the effect of diverting the blood in the extra-splanchnic area

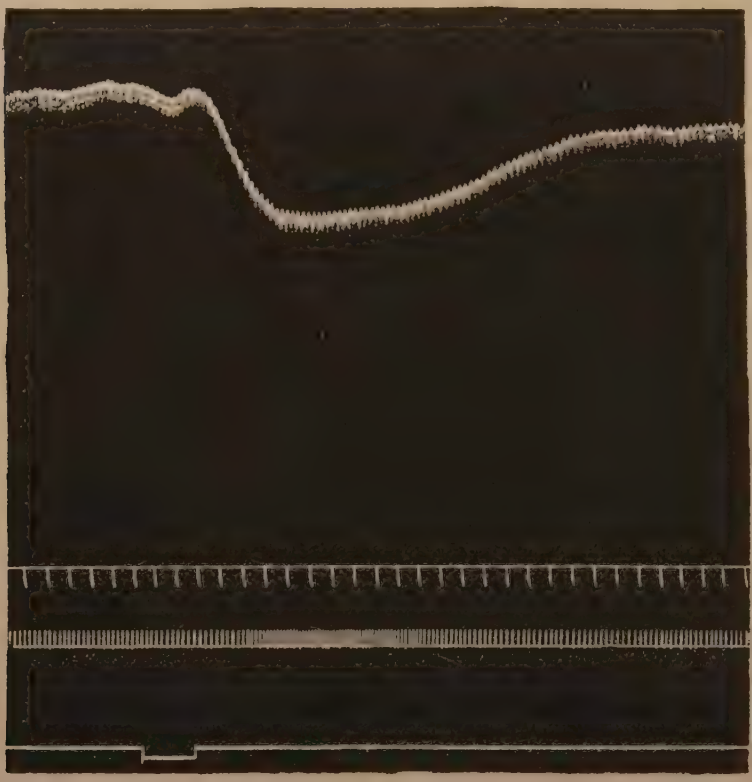

Fig. 7. Graph showing the effects of epinephrin upon venous outflow from leg of a dog. Dose, 0.5 c.c. 1:100,000 solution, by vein. The peroneal nerve was cut four days before and the sciatic previous to the beginning of the experiment. The upper line represents arterial blood pressure; the second line time at 5 second intervals; the third line, outflow of blood by drops; fourth line, signal. (After Gruber, Am. J. Physiol.)

from the skin to the skeletal muscle. This has an obvious bearing upon the "emergency theory" of suprarenal function.

Effects on the Circulation of the Liver.—The first important study of the effects of epinephrin upon the circulation in the liver was reported by Schmid (1909). A Stromuhr was inserted in the portal vein. It was found that immediately following the injection of epinephrin the volume of the portal blood-stream began to decrease, reaching its lowest point synchronously with the maximum rise of blood-pressure. A second

phase immediately succeeded during which the stream volume increased and attained the normal height at the same time as blood-pressure. The portal blood-pressure usually decreased during the early part of the reaction but later increased until it was considerably above the normal point. Certain exceptions to this behavior were noted. In one dog the portal stream showed no decrease in volume, but an increase to four times the normal. It was also found that under the influence of epinephrin the blood-pressure in the vena cava was increased, but this increase persisted for a shorter period than that in the portal vein. Hence back pressure from the vena cava could account only partially for the portal increase, this being due in the main to an action of epinephrin upon the liver vessels. Such action persists longer upon the hepatic vessels than upon those in other localities, since the aortic and caval pressures often returned to normal before the portal pressure had regained its antecedent level.

Burton-Opitz (1912) has also reported Stromuhr observations upon the hepatic circulation. His experiments were restricted to dosages intended to produce "reactions of moderate amplitude." As a matter of fact, relatively very large doses were employed, e.g., 2 to 5 c.c. of 1:10,000 solution of epinephrin, introduced by facial vein. In other experiments, however, in which the drug was introduced directly into the hepatic artery, 2 to 4 drops of the solution were found sufficient. Observations upon 8 dogs were reported. The method was to ligate the gastro-duodenal artery distal to the liver and to insert the Stromuhr into the hepatic artery very close to the right hepatic branch or into the portal vein. Blood-pressure in the femoral and the hepatic arteries was recorded simultaneously with the flow. The effect of epinephrin was determined both upon arterial and upon venous inflow in the liver.

It was found that simultaneously with augmented systemic blood-pressure there was an increased inflow in the hepatic artery, both reaching their maximum at the same time. Sometimes, however, the hepatic artery was so constricted by the epinephrin that the increased blood flow was brought to an abrupt end and in place of it there was a decrease which might give values strikingly below normal, even while the systemic pressure was still high.

As regards the portal inflow, epinephrin in small quantities was found to cause a slight retardation accompanied by a marked increase in the portal blood-pressure. If sufficient epinephrin was introduced into the portal vein to bring about changes in the general circulation, an initial increase in portal inflow was followed by a further subsequent increase dependent upon the augmented systemic blood-pressure. In some cases, however, augmented systemic pressure was noted without any corresponding increase in the portal flow. Ordinarily, the increased portal pressure persisted for some time after the systemic blood-pressure had regained a normal level. On account of the dissociation noted between pressure

changes in the general circulation and reactions in the portal circulation, Burton-Opitz was led to subscribe to the opinion that the portal vein is supplied with venomotor fibers.

Both Schmid and Burton-Opitz noted that there is a marked difference in reaction in different animals of the same species, some showing an increased and others a decreased inflow. The apparent explanation was offered that in some cases the liver vessels receive but little of the injected epinephrin as compared with other abdominal vessels, while in other cases a proportionately larger amount of the drug enters the portal circulation.

Edmunds (1915) subjected the problem to renewed study, making both plethysmographic and perfusion experiments. His work was done mainly upon dogs, though a few experiments upon cats also were reported. Blood-pressure from the carotid artery was recorded during the course of the plethysmographic studies. The epinephrin was injected into the femoral vein. "Small" doses (0.5 to 1 c.c. of 1:25,000 or 1:50,000 solution) were employed. A special type of plethysmograph was devised and adapted to the left lobe of the liver.

Edmunds' observations with the plethysmograph confirmed those of previous observers with the Stromuhr, in showing distinct differences in the manner of reaction to epinephrin by different dogs. The plethysmograph was found to have the advantage of showing definite circulatory changes of such brief duration as to escape detection by the Stromuhr.

Most commonly it was found that immediately after the blood-pressure began to rise the volume of the liver decreased and the contraction lasted throughout the period of the systemic reaction. The liver volume then gradually returned to normal, in this phase apparently passively following the blood-pressure. The vasomotor effect in the liver obviously persisted longer than in other parts of the body. An interesting variant of this reaction was seen in some dogs and proved to be the characteristic reaction in cats. In such animals no decrease whatever in liver volume was seen, but an increase which outlasted the rise in systemic blood pressure. Associated with this was an increase in the amplitude of contraction of the right ventricle. Edmunds accordingly interpreted the dilatation in the liver as due to a cardiac factor. In view of the active vasodilatation which has been demonstrated in other organs as a reaction to epinephrin, it would seem that the phenomenon is worthy of further study.

Edmunds attempted to simplify the problem by controlling the hepatic circulation while registering liver volume. Normal tracings were first taken and then the hepatic artery occluded and the tracing repeated. The result of clamping this artery was to bring all the various types of reactions and curves into a single group. The reaction now consisted of two phases. During the first twenty to thirty seconds following the injection of epinephrin there was either no increase in volume or a very gradual

increase followed by a more rapid increase. In the first phase no relation to the general blood-pressure could be perceived. The second stage of rapid increase in volume was often of considerable extent and it frequently lasted until long after the blood-pressure had fallen to normal.

A study was then made of the changes in portal blood-pressure and in vena cava pressure in relation to the liver volume changes. The portal pressure showed a preliminary fall followed by a considerable rise that was well sustained. The rise of portal pressure did not coincide with decreased liver volume, as would be the case if it were due to vasoconstriction in the portal system. The increased liver volume was ascribed chiefly to back pressure from the vena cava, since augmented caval pressure appeared at the time of the secondary volume reaction and persisted partially through it. The fact that the liver volume remained largely augmented after the caval pressure had returned to normal, Edmunds explains as due to sequestration of blood in the liver vessels. The published evidence that such is the case does not seem entirely convincing. The general trend of investigations on the relation of epinephrin to venous pressure is to indicate that well-marked systemic reactions, due in turn to local vasomotor effects, can take place without any significant change in venous pressure.

By direct perfusion experiments Edmunds was able to show that epinephrin may cause more or less vasoconstriction in the liver vessels. Similarly, by the application of epinephrin to isolated sections of portal vein, a reaction to the drug was proved.

Macleod and Pearce(*b*) (1914) have also reported venous outflow studies in the liver. They administered doses of 0.2 to 0.4 mg. of epinephrin through the pancreatico-duodenal veins of dogs. This caused an immediate decrease in the outflow. The result was practically the same, whether the hepatic arteries were ligated or not, a fact which indicates that the ramifications of the portal vein in the liver are supplied with vasoconstrictor fibers. These latter results are definitely of only pharmacological significance, the dosage far transcending physiological limits.

Bainbridge and Trevan (1917) corroborated earlier reports that the administration of epinephrin causes obstruction of the blood flow through the liver and if the infusion is sufficiently prolonged the animal passes into a condition of shock. The partial pressure was recorded from the splenic vein and caval pressure from the iliac. The recording manometer was filled with 3.5 per cent sodium citrate solution. The epinephrin caused an augmentation of liver volume and increases flow of lymph from the thoracic duct. Little or no change of caval pressure resulted, under the conditions of their experiments. The authors tentatively concluded that the obstruction was due to "narrowing of the capillary channels by swelling of the liver cells."

In connection with a study on shock, Erlanger and Gasser (1919) administered very large doses of epinephrin (e.g. 10 mg.) and noted the effects on the circulation in various parts of the body. They found that the portal blood pressure was invariably raised,—15 to 30 mm. Hg. This usually fell practically to a normal level after a time, even if the administration of the epinephrin was continued, often reaching this level while the arterial pressure was still high. Associated with this perturbation of the portal pressure was a very marked decrease of blood flow into the splanchnic area from which the portal circulation is derived. After considering the various possible explanations, the authors concluded that the elevation of portal pressure was due to increased "portal-hepatic resistance." The outstanding result of their work is that epinephrin markedly slows the circulation through the liver and supposedly produces some degree of asphyxia. In view of the enormous dosages of epinephrin administered, however, the results are of pathologic rather than of physiologic interest.

The foregoing evidence as a whole does not afford grounds for any very satisfactory conclusion as to what effect normal suprarenal discharge might have on the liver circulation. Stromuhr studies have shown sometimes an increased and sometimes a decreased flow. Plethysmographic studies have likewise given somewhat equivocal results. The problem is in need of further study with especial attention to the quantitative factors. Such studies have an obviously important bearing on the relation of the suprarenal glands to carbohydrate metabolism.

Effects on the Circulation of the Spleen.—In their original report on the pharmacology of suprarenal extracts, Oliver and Schäfer included certain observations on the spleen. In several cases studied the reaction of the extract was an "enormous" contraction. In no case was any dilatation observed except for a short time preceding the reaction proper. This was regarded as probably a passive effect. Bardier and Frenkel recorded the results of a study on a single animal that was apparently under the influence of curare. Their extract was made by macerating suprarenal gland for twenty-four hours at 37° C. Whether such an extract gave purely epinephrin effects is very doubtful. After three injections they noticed: (a) dilatation for three minutes followed by constriction while systemic blood-pressure arose from 110 to 220 mm.; (b) contraction followed by dilatation while the systemic pressure varied between 100 and 120 mm.; (c) dilatation followed by contraction while the arterial pressure varied from 80 to 180 mm. Judging from the sequence of initial arterial pressures recorded, the animal was relapsing into shock. The vasomotor reactions in the first and third cases indicate that the doses transcended physiological limits. Falta and Priestly observed that the spleens of animals exposed several hours after subcutaneous injections of large doses of epinephrin appeared anemic. Vincent, without giving any details,

states that epinephrin administered intravenously causes contraction of the spleen.

Hoskins and Gunning(*a*) (1917) studied the matter further. Dogs were used as the experimental animals. Ether or morphin-ether anesthesia was generally employed but a few animals were decerebrated. In some instances the vagi were cut but this procedure made no apparent difference in the outcome. Epinephrin was introduced into a femoral vein sometimes instantaneously and sometimes slowly. Various quantities were administered, giving pressor effects in some instances and depressor effects in others. Simultaneous records were made of changes in splenic volume or venous outflow, or both, and of changes of femoral arterial pressure. Observations were made upon 17 animals. In the plethysmograph studies 65 injections and 18 infusion experiments were made, while the venous outflow series included 34 injections and 20 infusion experiments. In nearly all cases a brief dilatation, supposedly passive, was followed by marked contraction. These results were independent of changes in systemic blood-pressure, being obtained both with depressor and with pressor dosages. It was found possible to hold a spleen in a state of uniform contraction by epinephrin infusion for a period of ten minutes. The effect in the spleen lasted from a half to five and a half minutes after blood-pressure had returned to normal. In no case, with either large or small dosage, was a secondary dilatation observed during an infusion period. Occasionally, however, dilatation occurred after the administration of the drug was discontinued. This effect was not passive, since it was noted when the arterial pressure was either normal or depressed. With no dosage was a pure splenic dilatation observed. The threshold for the reaction was highly variable but generally lower than that for changes of arterial pressure. The most sensitive preparation showed contraction with a dosage of 0.5 c.c. of a 1:2,000,000 solution, hence the spleen is one of the most sensitive organs in the body.

The effects on venous outflow were what might be expected from a consideration of the volume changes. During the preliminary dilatation the flow was augmented. The augmentation persisted during the first part of the contraction period while the blood already in the organ was being expelled. During the remainder of the contraction period the flow was depressed, reaching the normal rate at about the same time splenic volume was restored to normal. The depressed outflow during the latter part of the period was obviously due to retention of blood in the expanding organ (Fig. 8).

Hartman and McPhedran also reported studies on the effect of epinephrin in the spleen made about the same time as those of Hoskins and Gunning. Of 10 dogs investigated, 7 showed only constriction in the spleen in response to the whole range of doses of epinephrin administered. The constriction was more marked and more prolonged with in-

creased doses. Three of the dogs showed dilatation with some dosage of epinephrin. Two of the three showed as a first effect dilatation with small doses and the third showed a secondary dilatation following the constrictor effect.

The available evidence as a whole indicates that epinephrin produces as its only significant effect a contraction of the spleen which plays some part in the general shift of the blood from the splanchnic to the outlying circulation. This contraction may or may not be associated with dilatation of minor degree.

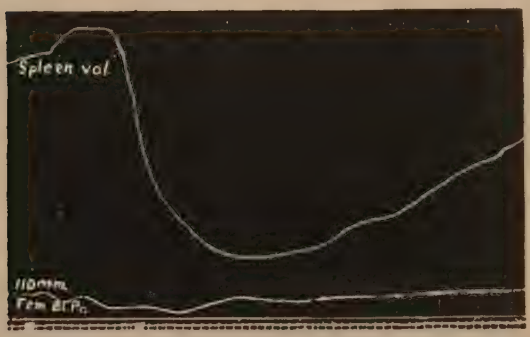

Fig. 8. Graph showing contraction of the spleen under the influence of epinephrin, depressor infusion. Dose, 2.8 c.c. 1:200,000 solution, administered by vein during a period of 65 seconds. Dog weighed 15 kilos. Time, 5 seconds. (After Hoskins and Gunning, Am. J. Physiol.)

It is interesting to note that the vasoconstrictor effect of epinephrin in the spleen lends aid in two diagnostic problems. A tumor in the splenic region can thus be differentiated from the spleen itself. A preliminary injection of epinephrin is said also to be useful in driving blood infested with malarial organisms from the spleen into the general circulation, thus facilitating their detection.

Effects on the Circulation of the Kidney.—The effects of epinephrin on vascular conditions in the kidney were first studied by Oliver and Schäfer, who noted a marked diminution in kidney volume.

Bardier and Frenkel (1899) investigated the relation of suprarenal extracts to diuresis, and included some studies of vasomotor effects. Their experiments were made on anesthetized dogs, apparently under the influence of curare. The extracts were made from either desiccated suprarenal glands or from fresh gland material macerated for twenty-four hours at body temperature. Judging from the reported effects on arterial pressure, relatively large doses were employed. The extracts were administered intravenously. The authors describe as typical effects contraction of the kidneys and depression of urine flow, followed by dilatation of the organ and diuresis. In certain exceptional cases, however, the injections were followed at once by dilatation and polyuria. Whether the presence of protein decomposition products, which may well have been present in their extracts, played any part in the results is not determinable from the data reported.

In the same year Gottlieb included the kidneys in a series of experiments on the effects of suprarenal extracts on the heart and blood vessels. His observations were made on isolated kidneys of hogs and

dogs. It was noted that when such extracts were added to the fluid which was being perfused through the organ, a marked decrease in outflow resulted. This finding was corroborated by Gioffredi. Similar experiments were made by Sollmann in 1905. When epinephrin in a dilution of 1:50,000 was perfused through the isolated kidney there was a marked decrease in venous outflow and of kidney volume, accompanied by a decreased urine flow. It may be noted that Sollmann used a solution from twenty to one hundred times as concentrated as the epinephrin in the blood of the lumbo-adrenal veins, as determined under ordinary experimental conditions. In three perfusion experiments Pari found that solutions of 1:20,000 to 1:100,000 caused renal vasoconstriction, but in one case a solution of 1:500,000 caused dilatation for a few minutes followed by constriction.

Jonescu (1908) recorded the effects of intravenous injections of epinephrin on the blood-pressure and kidney volume of rabbits. Doses which caused a moderate rise of blood-pressure caused a slight dilatation of the kidneys, which was followed by a marked contraction which persisted for some time after arterial pressure had returned to normal. With smaller doses renal contraction only was seen, the blood-pressure remaining practically unchanged.

In a short paper, published in 1911, Froehlich(*b*) reported that both *l*- and *d*-suprarenin, as well as "adrenalin," cause a protracted contraction of the kidneys. A more extensive investigation along the same line was reported a year later by Ogawa. He used both natural and synthesized epinephrin. Instead of the oncometer method employed by Froehlich, however, he utilized perfusions to determine the effect of the drugs on the kidney vessels. In the most sensitive animals a diminished outflow was observed with a dilution of *l*-suprarenin of 1:20,000,000. With a solution of 1:1,000,000 the primary effect was a sharp decrease in the rate of outflow followed by a rate above normal when the drug was discontinued. Augmented outflow was noted also as a secondary effect if the epinephrin perfusion was continued for a relatively long period. The secondary dilatation was seen only when the epinephrin was used in solutions of 1:1,000,000 to 1:5,000,000. In two instances primary dilatation was noted with solutions of 1:40,000,000 and 1:50,000,000, respectively. The same results were obtained with *d*- as with *l*-suprarenin, except that stronger solutions had to be used. The synthetic product gave reactions qualitatively similar to the natural. In cats and dogs the same results were obtained, but the thresholds were higher.

In all the foregoing reports renal vasoconstriction following the administration of epinephrin is the outstanding feature. In most cases, however, the doses employed were probably greater than the quantity that can be discharged from the suprarenal glands in corresponding periods of time. The evidence, so far as it goes, indicates that urine secretion

is depressed pari passu with the vasoconstrictor effect. This renders important, as bearing on renal physiology, a definite determination whether the vasodilatation reported by Bardier and Frenkel and by Ogawa is a significant feature of the response to epinephrin injection. If such dilatation is characteristic, then epinephrin diuresis (such as has been described by Kleiner and Meltzer) may be ascribed to local vasomotor effects in the kidneys. The fact that vasodilatation was observed only as a secondary effect with larger doses when the epinephrin would supposedly be largely destroyed, or as a primary effect only when very small concentrations were employed, points toward this as a physiological mechanism, since it is probable that the body normally has to deal with only very high dilutions. This might be correlated with the fact observed by Kleiner and Meltzer that in order to produce diuresis epinephrin must be administered so as to be slowly absorbed, whereas in cases in which it reaches the kidneys promptly it acts as a renal depressant (Cow, 1914).

In view of the important theoretical question involved, the relation of ephinephrin to renal circulation was further studied by Hartman and McPhedran and by Hoskins and Gunning(*b*) in 1917. Hartman and McPhedran made four oncometer experiments, two on cats and two on dogs. In every instance epinephrin caused vasoconstriction. With small doses this was the only effect. In two cases in which large doses were used, the contraction was followed by a secondary dilatation. This dilatation persisted a considerable period after blood-pressure had regained its normal level.

Hoskins and Gunning made determinations of volume changes or of venous outflow in sixteen dogs. In their experiments the outstanding feature of the reaction was a sharp contraction of volume (Fig. 9). In most instances this was preceded by a brief preliminary expansion, inconsequential in degree and interpreted as purely passive. The contraction outlasted for a half to two minutes the arterial pressure reaction. In one case only was a different type of reaction observed. In this, after the passive preliminary dilatation, as the blood-pressure rose the organ contracted; then, as arterial pressure began to fall, the kidney dilated and returned to its initial volume a minute after the normal blood-pressure was restored. This result was obtained when 0.5 c.c. of 1:100,000 solution was administered. When the dose was doubled the ordinary renal contraction picture appeared and outlasted the change of blood-pressure. In no case was a pure dilatation observed. It was found that the kidneys could be held for at least ten minutes in a uniform state of contraction. The threshold dosage for changes in kidney volume and for changes in blood-pressure were approximately the same. The reactions in the kidney were qualitatively similar, irrespective of whether pressor or depressor dosages were employed. The observations on venous

outflow consistently supported the reports of previous investigators that epinephrin causes a decrease.

Hartman and Lang subsequently reinvestigated the problem. They perfused the kidneys of two dogs, obtaining both constrictor and dilator effects, though constrictor effects predominated. Applying epinephrin directly to the semilunar ganglion in a rabbit gave only constrictor effects in the kidney. In cats no distinct vasomotor reactions in the kidneys could be obtained by hypodermatic injections of epinephrin (0.5 mg.).

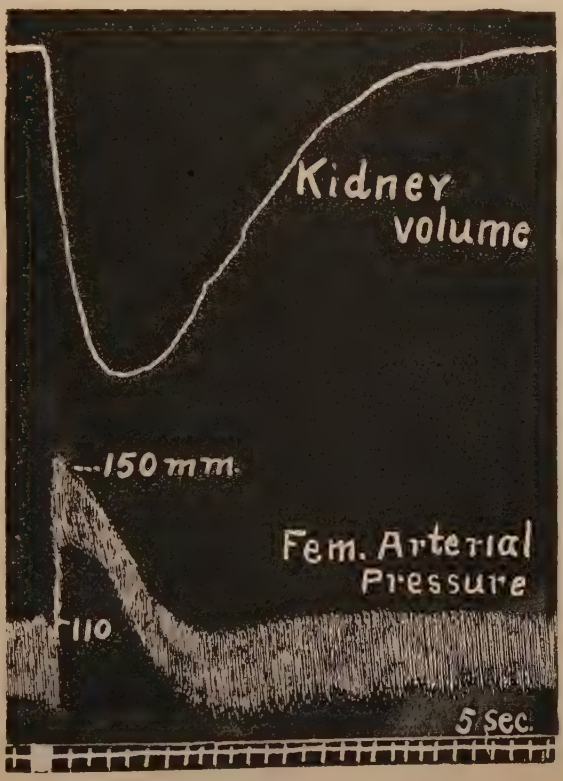

Fig. 9. Graph showing contraction of the kidney under the influence of a pressor dose of epinephrin, 4.0 c.c. 1:100,000 solution by vein. Pulse and blood-pressure records from femoral artery. Dog weighed 18 kilos. Time, 5 seconds. (After Hoskins and Gunning, Am. J. Physiol.)

The sum total of available evidence fails to support convincingly the theory that epinephrin diuresis is due to a dilator effect of this drug in the kidney. On the other hand, the data do not definitely exclude the possibility that such may be the case in normal unanesthetized animals. In view of the evidence that epinephrin in doses causing renal vasoconstriction depresses urine formation; that epinephrin administered subcutaneously, and, consequently, absorbed slowly, causes polyuria; and that in anesthetized animals renal vasodilatation has occasionally been reported following the administration of epinephrin in high dilutions or as a secondary reaction with larger quantities, the theory is not untenable that in normal animals epinephrin in relatively small quantities causes dilatation in the kidneys. The problem demands further study.

Effects on the Circulation of the Intestine.—As in case of various of the other organs previously discussed, the first observations on the effects of suprarenal extracts on intestinal circulation were made by Oliver and Schäfer. They made no direct determinations but concluded from inspection that vasoconstriction in the gut wall results from the intravenous in-

jection of such extracts. The generalization was offered that vasoconstriction is caused throughout the splanchnic area. Elliott has reported a single instance in which he applied epinephrin directly to the wall of the intestine of the fowl, and also gave an intravenous injection. The result, as determined by inspection, was an intense vasoconstriction.

Apparently the first to make a more accurate study of the problem was Frochlich(*b*) (1911). He enclosed a segment of intestine in a plethysmograph and noted the effects of both *d*- and *l*-suprarenin, as well as "adrenalin." In both cats and dogs a long-lasting contraction of the gut was observed. Few details regarding the experiments were reported. Vincent in his monograph states that sometimes the intestine expands under the influence of epinephrin; and he publishes a plethysmographic curve, which shows a slight degree of expansion that might be interpreted as passive.

Perfusion studies were made upon vessels of the isolated intestine by Brodie and Dixon (1904). The addition of epinephrin to the perfusion fluid materially decreased the venous outflow. They found that dosages as small as 0.0001 mg. were effective. Ogawa (1912) has reported the results of similar studies. He worked upon rabbits, cats, and dogs. His findings were that the levorotatory form of epinephrin in greater concentration than 1:5,000,000 caused a clean-cut constriction in the intestinal vessels, as was shown by a decreased venous outflow. With higher concentrations of this general magnitude, occasionally a secondary dilatation was observed. In higher dilutions, e.g., 1:50,000,000, the effect was primary dilatation. It was found that the dextrorotatory form had a similar effect but larger doses were required.

Hartman and McPhedran (1917) reported further plethysmograph studies, using dogs and cats as the experimental animals. A loop of small intestine, about a third of its total length, was isolated with care to protect the circulation and placed in an oncometer. In most cases the effect of epinephrin in both large and small doses was primarily to cause constriction of the intestine. With the smaller doses this was almost invariably the effect. As the quantity was increased, however, a prolonged and marked dilatation succeeded the preliminary constriction (Fig. 10). In two exceptional cases studied by these investigators the least effective dose caused at least apparent dilatation; in these, there was some probability of experimental error. The threshold for the constrictor effects was found to vary within fairly wide limits,—from 0.014 to 0.07 c.c. of 1:100,000 solution per kilogram of body weight. These dosages were slightly depressor. That the contraction of the intestinal segment was not merely a passive effect due to the lower arterial pressure, however, appeared from the fact that the intestinal decrease preceded that of arterial pressure, that the lowest points of the plethysmographic and blood-pressure curves did not correspond, and that the duration of the effect in the intestine was quite different from that on systemic pressure.

Furthermore, constriction of the intestine was often seen when arterial pressure was elevated above the normal.

The amount of epinephrin required to bring about dilatation of the intestine was also found to be quite variable. The range of dosage was from 0.04 to 0.4 c.c. of 1:1,000,000 solution per kilogram. The latent period of the dilatation was longer than that of the constriction, and the constrictor effect seemed to be superimposed upon the dilator. As the dose was increased the resulting constriction became more and more marked and prolonged. When, however, the dosage passed the threshold for the constrictor effect, the dilatation phase was shortened by one-fourth to two-

Fig. 10. Graph showing preliminary contraction followed by prolonged dilatation of the intestine of a dog following injection of 0.2 c.c. 1:10,000 solution epinephrin. (Reduced one-third.) (After Hartman and McPhedran, Am. J. Physiol.)

thirds of its former length. As in case of the constrictor effect, it was not possible to correlate the dilator effect with changes in arterial blood-pressure.

When the sympathetic ganglia were removed or the splanchnic nerves were cut, the dilator effect of epinephrin was entirely done away with, only constriction then being elicitable.

Similar investigations were reported by Hoskins and Gunning (1917). These investigators, in addition to volume studies, determined the venous outflow. Their experiments were made in all cases upon dogs. The results are summarized in the accompanying table. The most prominent features of their findings as a whole were augmentation of the intestinal volume and of outflow from the opened veins. Often, however, the dilatation phase was preceded by a more or less pronounced contraction and in some instances contractions only were obtained. In case of the venous outflow the results were somewhat more consistent, augmentation always being noted, but this was not infrequently preceded by a decrease during

EFFECTS OF ADRENIN IN THE SMALL INTESTINE

	NORMAL		AFTER ECK FISTULA	
	Number of cases	Average dose	Number of cases	Average dose
		mgm.		*mgm.*
1. On volume				
a. Injections				
Pure contraction	9	0.013	0	
Pure dilatation	52	0.021	7	0.034
Contraction followed by dilatation	90	0.023	52	0.026
Dilatation followed by contraction	0		0	
		mgm. per minute		*mgm. per minute*
b. Infusions				
Pure contractions	2	0.011	0	
Pure dilatations	15	0.030*	8	0.043
Contraction followed by dilatation	14	0.036	11	0.046
Dilatation followed by contraction	0		0	
		dose in mgm.		*dose in mgm.*
2. On venous outflow				
a. Injections				
Pure augmentation	9	0.020	0	
Diminution followed by augmentation	31	0.025	2	0.020
		mgm. per minute		*mgm. per minute*
b. Infusions				
Pure augmentation	4	0.030*	0	
Diminution followed by augmentation	6	0.030	2	0.050

* Excluding one case of very low irritability.

the first part of the reaction. There was no very definite correlation between the dosage and the reaction. In some animals smaller quantities caused contraction, which was succeeded by dilatation as the dosage increased. In other animals, however, the reaction remained constant except as to degree, whatever quantity was injected. The range of doses investigated was about the same as that employed by Hartman and McPhedran. The threshold of reaction in the intestine was found in general to be about the same as that of blood-pressure. There was no constant relation, however, between blood-pressure and intestinal volume changes. The volume changes usually persisted after the blood-pressure returned to normal, indicating reflex compensatory adjustments among various organs. An after-dilatation of the intestine was frequently noted when the primary epinephrin effect had worn off.

In view of the fact that other investigators had reported that epinephrin may check the blood flow in the portal veins, the question arose to

what extent the volume reactions in the intestine might be dependent upon back pressure from the liver. To answer the question several dogs were tested before and after the production of an Eck fistula. It was found that shunting the portal blood directly into the vena cava ordinarily made no perceptible difference in the gut volume or venous outflow reactions. The liver, therefore, played no essential rôle.

More recently Erlanger and Gasser (1919) have recorded some further observations on the effects of epinephrin in the splanchnic area. Their studies took account more particularly of the effects on the rate of blood flow in the various organs. They concluded that the effect is invariably vasoconstriction. In some cases this was so marked as to bring about almost complete stoppage of the blood. The discrepancy between their observations and those of the previous observers is supposedly to be ascribed to the fact that they used such enormous doses as 10 mg., that is, approximately a hundred times as great as those used in the earlier researches. Such data are obviously of merely pathologic, not physiologic, significance.

The available data as a whole do not permit any very satisfactory generalizations regarding the effects of epinephrin on the intestinal circulation. On teleological grounds one would expect the administration of the drug to result in vasoconstriction, since it produces (except in very minute doses) a striking inhibition of peristalsis; as a general rule, a quiescent organ receives a diminished blood supply. Furthermore, if, as Cannon maintains, epinephrin serves normally to integrate the body for strenuous muscular activity, this would be subserved by a shifting of the blood from the splanchnic area in general to the more active tissues.

It is possible that the dilatation reactions observed in the gut by some investigators may have been due to the employment of experimental methods inadequate to deal satisfactorily with the somewhat complicated circulatory conditions involved. It is possible too that merely opening the abdomen and manipulating the intestines may introduce such perturbations of the delicate physiological adjustments as to lead to anomalous results. In any case the problem needs further study. Erlanger and Gasser's inflow method, with proper attention to dosage, would perhaps be most likely to afford convincing data.

It is generally assumed, though without definite proof, that the circulatory reactions to epinephrin in the stomach parallel those in the intestine. It is also assumed that reactions in the large and the small intestine are similar. Both these assumptions should be put to the experimental test.

Effects on the Circulation of the Brain.—In view of the fact that the brain is incased in the rigid cranium, it can dilate or contract only as cerebrospinal fluid is displaced into or from the spinal canal. This can occur only to a very limited extent. Hence, gross vasomotor reactions to

epinephrin in the brain as a whole would not be expected, or possible. That epinephrin does produce some effect in the vessels of the exposed brain, however, has been demonstrated. Spina (1897) showed that intravenous injections of the drug result in marked dilatation of the cerebral vessels (Biedl). This obviously might be explained as a passive result of the general increase in arterial pressure. Biedl and Reiner showed that direct application of epinephrin to the cerebral vessels induces contraction. This contraction was overcome, however, when epinephrin reached the general circulation and caused increase in tension. Wiggers(*a*) (1905) perfused the cerebral vessels with Locke's solution to which epinephrin was added. This resulted in contraction of the blood-vessels. Thus it is evident that these vessels are capable to some extent of reacting to epinephrin and that the reaction is primarily in the direction of contraction,—at least with larger doses. So far as the writer is aware no determinations have been made of the reaction under approximately normal conditions. The quantitative relationships are especially in need of further study.

Effects of Epinephrin on the Heart.—The work of Oliver and Schäfer and of the other earlier observers showed conclusively that epinephrin has a marked stimulating effect upon the cardiac tissue. This effect may be and often is more or less masked by concomitant stimulation of the vagus mechanism, whereby the heart is depressed. These facts have long since become commonplace observations in student laboratories of pharmacology and physiology. That the stimulating effect of epinephrin in the heart as elsewhere depends upon the influence of the drug upon the sympathetic nerve terminals is generally believed. Biedl has offered direct evidence that such is the case. He studied the effects of epinephrin upon the heart of the embryo chick and found that it failed to respond to epinephrin until its sympathetic innervation was established.

Burridge (1917) has studied the effects of epinephrin on the heart in relation to the various inorganic salts present in the blood-stream. When frogs' hearts were perfused with saline solutions he found that traces of epinephrin render the balance between the inorganic constituents of such solutions of secondary importance as regards their suitability for the maintenance of cardiac activity. Unbalanced Ringer's solution, which contained too much calcium, too little calcium, or a considerable amount of potassium, interfered with the cardiac activity. Traces of epinephrin, however, rendered such unbalanced solution capable of maintaining cardiac activity and of preserving in great measure the resemblance between the behavior of the heart perfused with these solutions and with blood. Burridge believes that traces of epinephrin are constantly supplied to the blood and play an important rôle in facilitating cardiac functions.

It has been claimed by Danielopolu and Danulescu (1916) that epinephrin may exert a strikingly beneficial effect in heart block. To a patient

having a 2:1 rhythm they administered small doses of the drug and reported that the dissociation almost entirely disappeared in four minutes. Other observers, however, have not been able to substantiate this claim. Hardoy and Houssay (1917) administered epinephrin to a dog with experimental heart block and to two patients. They found that both the auricles and the ventricles were stimulated but in different degrees. It so happened that the changed rhythms caused the auricular and ventricular beats occasionally to assume a normal temporal relationship to each other and thus brought about the appearance of brief reconstitution of the normal rhythm. Arrillaga (1919) studied six cases of clinical auriculo-ventricular dissociation by means of the electrocardiograph. Reconstitution of the normal rhythm was not observed in any case. Ordinarily the reaction of the auricles and ventricles occurred simultaneously, but occasionally the ventricles reacted first. This observation is of interest in that it confirms in man the fact noted in the various experimental animals that epinephrin acts not merely upon the "pace-maker" but upon the auricles and ventricles more or less independently.

In man, as will be discussed in subsequent paragraphs, epinephrin ordinarily produces acceleration of the pulse. In dogs deeply anesthetized, especially if morphia is used, a similar acceleration is sometimes noted. In the laboratory animals generally, however, under conditions of ordinary anesthesia, the usual effect is depression of the pulse rate. This probably results to a considerable extent from reflexes set up by the high blood-pressure, particularly in the proximal aorta, which are mediated through the vagus nerve. That the high blood-pressure is not the only cause of the slowing, however, has been shown in different ways. Brooks, McPeek, and Seymour (1918) interposed in the blood-stream a reservoir bottle connected with the aorta. Under conditions which ordinarily would produce a rise in arterial pressure, blood flowed into the reservoir and the pressure was thus kept at approximately a constant level. It was shown that epinephrin injected under such conditions caused both slowing of the heart and increased amplitude of the beat. Brown (1916) studied the effect of epinephrin applied to the vagus center directly. He perfused the medulla of dogs with a mixture of defibrinated blood and saline solution through the carotid and vertebral arteries. When epinephrin was introduced into the perfusion mixture, slowing of the heart occurred immediately, before any reflex mechanisms resulting from changes of blood-pressure could come into play. Heinekamp (1919) carried out somewhat similar experiments with turtles. He perfused the head independently, leaving it connected with the body only through the vagus nerves. The introduction of epinephrin under these conditions also caused slowing of the heart.

Reaction of human subjects to epinephrin has been studied extensively by clinicians in recent years. Clough (1920) has summarized the litera-

ture and added numerous observations of his own. It is found that there is a marked difference in the cardiovascular reaction of different subjects to epinephrin when injected either subcutaneously or intramuscularly. The dosage has usually been 0.5 or 1.0 mg. Clough has classified the reactions arbitrarily, according to their intensity, as negative, moderate, marked, and very marked. In the moderate reaction there was a rise of systolic blood pressure of from 15 to 30 mm. of Hg associated usually with a fall of from 10 to 20 mm. in diastolic pressure. The striking feature of the reaction was the increase in pulse pressure which was often doubled. Despite the increased blood pressure, the pulse was usually quickened. In marked reactions the systolic pressure rose from 30 to 100 mm. There was usually a slight rise in diastolic pressure also and a marked rise in pulse pressure. When atropin was administered to block the vagus impulses, the reaction was often augmented. Further details regarding the effect of epinephrin on the pulse rate will be found in the chapter, "Clinical Tests for Thyroid Disorders."

In view of the stimulating effect of epinephrin upon the heart as a whole, its effect on the coronary circulation is of particular interest. A priori, dilatation would be expected in order to afford a greater blood supply to the cardiac muscle during the period of increased activity. Perfusion experiments by the earlier investigators showed that dilatation results in most experimental animals from the application of epinephrin.

Simple perfusion experiments in themselves are not, however, entirely conclusive, since the coronary flow may be influenced more or less by the reaction in other parts of the cardiovascular system. Morawitz and Zahn (*a*) (*b*) restudied the problem in the intact animal, using hirudinized cats and dogs as subjects. A catheter was inserted through the right auricle into the coronary sinus. The blood thus collected, after being measured with a recording device, was returned to the jugular vein. Epinephrin was found to cause augmented flow quite out of proportion to the increase in general arterial pressure.

Barbour (1912) obtained evidence, however, that in man epinephrin exerts a different effect upon the coronary arteries from what it does in the laboratory animals. It was demonstrated that isolated rings of the coronary arteries, obtained from subjects shortly after death, responded to epinephrin by contraction only. The experiments were controlled by the use of similar rings from calves, sheep, and pigs. These all responded by relaxation.

In view of the somewhat anomalous reaction observed in man, Barbour and Prince (1915) reinvestigated the problem in another primate, the *Macacus rhesus,* the experiments being controlled with rabbits. Isolated hearts were employed, these being perfused with diluted blood to which hirudin was added. The heart was excised immediately after death and connected with the aortic cannula of the perfusion system. Injections of

epinephrin were made into the rubber tubing near the aortic cannula. Perfusion pressures of 50, 75, and 100 mm. of mercury were employed, the temperature of the fluid being held constantly at 38° C. In the rabbit doses of epinephrin varying from 0.025 to 0.25 mg. were used. In the monkeys the dosage varied from 0.025 to 2 mg. In the rabbits the reaction was always increased coronary outflow. In the monkeys the results, on the other hand, were precisely the opposite, decreased flow. This decrease was obtained under all conditions of high or low perfusion pressure, with beating or resting hearts, and with all effective doses.

The same criticism may be offered against these as against many other experiments upon the pharmacology of epinephrin, namely, that concentrations grossly out of proportion to those to which the tissues are exposed under normal conditions were employed. So far as the writer is aware, no experiments upon primates have been recorded in which the quantitative factor received due consideration. Moreover, before the conclusion can be definitely accepted that epinephrin causes coronary constriction it will have to be demonstrated in the intact animal with conditions kept as nearly physiologic throughout as possible.

Effects of Epinephrin upon Pulmonary Circulation.—The first direct studies of the effects of epinephrin on the pulmonary circulation were made in 1904 by Brodie and Dixon and by Plumier(*a*). The latter experimented with dogs under morphin-chloroform anesthesia. Monometers were connected with the carotid artery, the pulmonary artery, and the right auricle. Epinephrin, in doses of 0.5 to 1.0 mg., was administered intravenously. This resulted in an increase in both the pulmonary and in the carotid blood-pressure, as well as the pressure in the auricle. That the increased pulmonary pressure was not a "backing-up" effect was shown by cutting the vagi. Under these conditions the augmented pressure in the left auricle no longer appeared but increased pulmonary pressure persisted. Plumier also noted the effects of epinephrin on the venous outflow from the lung perfused with defibrinated blood. The addition of epinephrin in rather large quantities (0.5 mg.) caused a marked decrease in the outflow.

Brodie and Dixon's studies were very similar to those of Plumier, except that they used relatively smaller doses. Isolated lungs of dogs, cats, and rabbits were perfused with the animal's own defibrinated blood. The addition of such quantities of epinephrin as 0.05 mg. produced either no effect or an increased outflow. Wiggers(*b*) (1909) reported similar experiments upon the lungs of three dogs and one rabbit; he perfused one lobe at a time. The experiment was brief in each case to forestall the effects of edema. As a menstruum, either Locke's solution or gelatin in sodium chlorid solution to give a viscosity equal to that of the blood was used. When the viscosity factor was thus controlled, only constrictor

effects were obtained. The minimal dose used was 0.02 mg. Campbell (1911) reported twelve perfusion experiments upon cats and rabbits. In most cases he obtained slight diminution in the outflow. Baehr and Pick (1913) obtained no distinct effect when Tyrode's solution containing 0.01 mg. of epinephrin per liter was perfused through guinea-pigs' lungs. Führer (1913) noted constriction as the result of perfusing isolated dog's lung with epinephrin solution. Tribe (1914) reported an extensive series of perfusion experiments upon the lungs of cats, dogs, rabbits, guinea-pigs, rats, and ferrets. She used defibrinated blood as the perfusing medium. With dilute solutions (0.00002 mg.) dilatation was obtained, while with larger doses (0.01 mg.) constriction resulted. Schafer and Lim (1919) have reinvestigated the problem very carefully. Cats and rabbits were used. The range of dilution of the epinephrin was from 1:2,000 to 1:62,000. In nearly every case constriction resulted.

Thus most observers who have studied the problem have found that epinephrin results in constriction of the pulmonary blood vessels. In a few instances, however, dilatation has been reported. This has resulted from the smaller doses and such as supposedly approach the physiological. As nearly as data now available permit one to judge, the concentration of epinephrin used by most of the observers was hundreds or thousands of times as great as that in the normal blood-stream. The data are of correspondingly slight *physiological* significance.

The effects of epinephrin upon the pulmonary circulation of the living animal have been studied by a number of observers. Cybulski (1897) is quoted as having noted that intravenous injections of suprarenal extract produced a slight rise of pulmonary pressure, which was ascribed to back action from the systemic vessels. He worked on dogs under the influence of curare. Velich(*b*) (1898) obtained similar results, as did also Gerhardt (1900). Mellin (1904) recorded the effects of epinephrin upon the pulmonary and aortic blood-pressures simultaneously, using curarized rabbits as experimental animals. He found that epinephrin in quantities sufficient to cause a great rise of systemic blood-pressure had practically no effect upon the pulmonary circulation. Plumier, as previously noted, obtained marked increase in both pulmonary and systemic pressure, but he used relatively enormous doses. Rise in pulmonary pressure under the same conditions has also been noted by Pettijean (1908) and by Weber (1910). Desbouis and Langlois (1912), having noted the reports of earlier investigators that reversal in the systemic blood-pressure reactions to epinephrin can be obtained by changing the dosage, investigated this point in relation to the pulmonary circulation. Using an electrical method, they determined the rate of blood flow through the lungs of the dog. With smaller doses, 0.025 or 0.05 mg., accelerated flow was noted. With larger doses, as 1 mg., marked retardation of the flow was seen. Similar results had been reported by Edmunds (1907). Anderes and Cloetta (1916) came to the

conclusion that epinephrin ordinarily has no effect upon the pulmonary circulation.

Schafer and Lim (1919) have reinvestigated the problem, using cats, dogs and rabbits as experimental animals. Epinephrin was administered sometimes by jugular vein, sometimes by carotid artery. Elaborate precautions were taken to rule out the effects of adventitious factors. Both pulmonary and systemic blood-pressure was recorded. They found that in the rabbit epinephrin injected in moderate doses into the jugular vein caused at first either a rise of pulmonary blood-pressure due to constriction of the pulmonary arterioles, or no effect. But when the drug reached the systemic arterioles the rise in systemic pressure that ensued was accompanied by a fall in the pulmonary pressure, with gradual return to normal as the constriction in the systemic vessels disappeared. Similar results were sometimes seen in the cat, but the usual result was a well-marked rise in pressure in both the pulmonary and systemic arteries. With unusually small doses a fall of pressure was seen in each system. In the dog, intravenous injections of fairly large doses resulted in a great rise of pressure in both systems, sometimes running almost parallel, sometimes better marked in the pulmonary than in the systemic arteries. In all three animals, when the injections were made by vein, the pulmonary rise was sometimes very distinctly in advance of the systemic, and when injection was made into an artery the systemic rise appeared first. In many animals, however, the rise was simultaneous in each system. The rise in pulmonary pressure could not be ascribed to back pressure from the aorta because, in some instances, marked increase in the aortic system was noted with no rise whatever in the pulmonary pressure and because of the temporal relations of the reactions. The chief effects in the rabbit were ascribed to the constricting influence of the drug upon the blood vessels of both systems, but in most cats and in dogs the effect appeared to be due chiefly to action on the cardiac musculature.

The sum total of the available evidence would seem to indicate that the effects of epinephrin in the lungs are not such as to influence markedly the general circulation. With large doses, some degree of pulmonary constriction occurs, but this would seem to be sufficiently compensated for by the concomitant stimulation of the heart. With smaller and supposedly more nearly physiologic quantities, some degree of dilatation, and hence perhaps of freer blood flow in the pulmonary vessels, results. The data as a whole afford no substantial basis for teleological speculation.

When very large doses of epinephrin are administered by vein to an intact animal the pulmonary circulation is sometimes overwhelmed, with resulting acute edema of the lungs. Seldom is an investigator confronted with so striking a picture as that presented by this condition. Its onset is almost instantaneous. Blood-stained froth begins to flow from the respiratory orifices in a voluminous stream. Respiration at first is labored

but soon subsides as the animal drowns in its own exudate. The possibility of such an outcome should be kept in mind in the therapeutic use of epinephrin in any condition in which failure of the right heart threatens.

Effect of Epinephrin upon Venous Pressure

Venous pressure may be increased in a number of different ways. The three chief possibilities are by interference with the flow into the thoracic cavity, by a decrease in the peripheral resistance, allowing relatively more blood to pass from the arterial to the venous side, and by a decrease in the caliber of the veins themselves. The flow into the thorax may be impeded either by factors which interfere with respiration or by factors which depress cardiac efficiency. Epinephrin conceivably may affect venous pressure by modifying any of these factors.

That epinephrin may directly stimulate the veins to contraction has been shown by a number of observers. Gunn and Chavasse (1913) applied epinephrin (1:100,000 solution) directly to isolated ring preparations from various veins of the sheep. These included the external jugular and mesenteric veins, and the superior and inferior venæ cavæ. They noted constriction similar to that which occurs in artery rings under like conditions. The external jugular contracted more extensively than did the cavæ. It was concluded that the veins probably receive venoconstrictor fibers from the sympathetic nervous system. Crawford and Twombly, in the same year, publiished observations corroborating the findings of Gunn and Chavasse. They worked with ring preparations from the femoral, iliac, and saphenous veins of the dog, noting contraction in each. In case of veins from fowls, however, some veins were found to contract and others to fail to do so.

Other observers had previously investigated the problem by making intravenous injections of suprarenal extract or epinephrin and measuring the pressure reactions in the large veins. Hill (1900) found that the administration of sufficient suprarenal extract to a vagotonized dog to cause a rise in arterial pressure of 1170 mm. of magnesium sulphate solution left the pressure in the vena cava unchanged. Plumier(b)(1909) administered epinephrin to the intact dog and noted a rise in the pressure in the superior and inferior venæ cavæ. This he attributed to the slowing of the heart which ensues under the conditions of his experiments. The fact that the rise in caval pressure was not so great as might be expected from the slowing of the heart that was produced, he interpreted as due to increased force of the heart beat. After cutting the vagi, unless very large doses were administered, there was little or no change in venous pressure. This was true in spite of the fact that the marked vasoconstriction resulting from the epinephrin administered materially decreased the

capacity of the arterial system, a factor which in itself would tend to shunt the blood into the veins. Capps and Matthews (1913) found that small doses of epinephrin do not affect venous pressure, but that larger doses, such as 0.12 mg., cause a rise of from 10 to 80 mm., which coincides with marked slowing of the heart. The persistence of the augmented venous pressure coincided with that of the cardiac reaction. Since they obtained a similar effect from faradizing the vagus nerve, they concluded that the rise in venous pressure is to be attributed to the cardiac factor rather than to any venomotor influence of the epinephrin. Bainbridge and Trevan (1917) administered epinephrin after paralyzing the vagus terminals in the heart with atropin. Under these conditions they found little or no change in vena cava pressure when epinephrin was injected. They noted, however, a considerable rise of pressure in the portal vein, which they attributed either to a swelling of the columns of the liver cells narrowing the capillary channels, or a constriction of the radicles of the portal vein. They found that 0.2 mg. of epinephrin caused a rise in the portal pressure of 255 mm. of sodium citrate solution. Kuno also administered epinephrin at a rate which caused accelerated heart-beat and obtained a slight increase in the venous pressure. This he attributed to relative narrowing of the arterial system, forcing more of the blood than normal to the venous side.

Erlanger and Gasser, in connection with their studies on circulatory failure due to epinephrin, made a few determinations of venous pressure. They used relatively very large doses of the drug administered by vein. In one experiment the jugular pressure changed but little, in two it fell, and in two it rose.

More recently Connet has investigated somewhat extensively the effects of epinephrin on venous pressure. Her experiments were made on about 50 dogs and 25 cats. The dogs were anesthetized with ether and the cats decerebrated. Arterial pressure was recorded with a mercury or a Hürthle manometer and venous pressures from the superior and inferior cavæ were read off from manometers filled with sodium citrate solution (2 per cent). Respiration was also graphically recorded. Epinephrin was injected by vein in quantities sufficient always to cause a rise in arterial pressure. In order to rule out effects due to changes in respiratory movements curare was administered in some cases. In the curarized, decerebrated cat, such dosages as 0.15 mg. caused an increase in arterial pressure from 34 to 167 mm. of mercury, leaving the pressure in the vena cava unchanged. In one unusual case a fall of venous pressure was noted. In some cases the increase in venous pressure was found to occur to approximately as great extent after as before curarization, hence the author concludes that the respiratory factor plays a minor rôle. In some cases the heart rate was increased, in others decreased. Under both conditions augmented venous pressure was seen. In some experiments

in dogs the vagi were cooled by the application of glass tubes through which ice water was circulating. The nerves were then allowed to return to room temperature. The pulse rate, arterial pressure, respiratory rate and amplitude were all affected, but little change in venous pressure occurred. The data as a whole were regarded as indicating that in the anesthetized dogs the venopressor mechanism played very little part. The rise in venous pressure was ascribed predominantly to decreased capacity of the arterial system and slowed heart rate.

In experiments on decerebrated cats, however, clear evidence was obtained of the operation of the venopressor mechanism. With the vagi intact, there was a rise of arterial pressure and slowing of the heart accompanying the rise in venous pressure. With the vagi cut, the cardiac factor being thereby eliminated, the rise in venous pressure was still produced. Since the respiratory movements were decreased in height and frequency, a condition which would tend to lower rather than raise venous pressure, the venomotor mechanism would seem necessarily to have to be invoked to explain the venous rise.

One gathers from the somewhat involved presentation that Connet's data as a whole indicate that epinephrin, administered in doses to cause a clean-cut rise in arterial pressure, results almost uniformly in augmented venous pressure. This augmentation is due in varying proportions to contraction of the arterial bed, interference with the cardiac output, changes in the respiratory rate, and stimulation of sympathetic fibers causing contraction of the veins themselves.

From the foregoing evidence it would appear that epinephrin, at least in such quantities as those with which the body normally has to deal, exercises little influence upon venous blood-pressure. Venous pressure changes, therefore, apparently play at most a minor rôle in the general circulatory reactions to this substance.

Factors Modifying the Pressor Response to Epinephrin

In connection with the discussion of the vasodilator effects of epinephrin, and in subsequent paragraphs the action of certain factors in converting depressor reactions to pressor is discussed. Obviously, a reversal of any of the conditions mentioned would result in the conversion of pressor to depressor reactions. The first effect in this latter case would be a decrease in the pressor response. Other conditions modifying the reaction to epinephrin have been reported.

In any condition in which the sympathetic system becomes abnormally irritable the response to epinephrin is of course increased. This fact forms the basis of the well-known Goetsch test for thyroid disorders. The data on this point are discussed in the chapter on "Tests for Thyroid

Disorders." It has been found by Hoskins and Wheelon that parathyroid extirpation is one means of augmenting sympathetic irritability that renders the animal (dog) more sensitive to epinephrin as it does to other sorts of stimulation.

Baraden (1916) made a series of investigations upon the vasoconstrictor mechanism, using the perfused ear of the rabbit as a test object. He found among other things that phosphorus poisoning results in the diminution of the vasoconstrictor effect of epinephrin.

Simonds (1916) reported an extensive series of observations on the condition of the vasomotor mechanism in dogs subjected to anaphylactic shock and peptone poisoning. He tested the condition of the peripheral structures by the administration of standard doses of epinephrin, such as before the poisoning evoked clean-cut pressor reactions. Following the poisoning, the reaction was found to be much diminished or entirely lost.

Schiff and Epstein have found that general debility may materially modify the reaction. Children with normal pulse quality were observed to react to epinephrin with a marked increase in blood pressure. On changing from the upright to the horizontal posture, the blood-pressure remained unchanged. Pale children with pulse of poor volume and tension, but without appreciable vasolability, reacted to epinephrin with a minimal increase of arterial pressure or with none at all. On lying down the blood-pressure was somewhat increased. Pale children with pulse of poor tension and volume but with apparent vasolability showed a prompt but very slight pressor reaction to epinephrin and no change in blood-pressure when the recumbent posture was assumed. These data were interpreted as indicating that in the debilitated children there is a functional inferiority of the vascular system leading to defective response to stimulation of the vasomotor innervation.

Collip(*a*) (1920) reported that the pressor reaction to epinephrin is augmented and prolonged by the administration of tissue extracts. He worked upon dogs and rabbits under ether anesthesia. The method in brief was to determine the reaction to a standard dose of epinephrin and then to administer intravenously extracts of such tissues as spleen, skeletal muscle, and parathyroid glands, and to follow this with the standard dose of epinephrin. In a typical case it was found that 3 c.c. of the drug in 1:50,000 dilution produced in a dog a rise of pressure of 32 mm. with a return to normal in 40 seconds. Five minutes after the administration of 25 c.c. of extract of ox spleen, the same dose of epinephrin caused a rise of 52 mm. in pressure with a return to normal within four minutes. Collip ascribes this augmenting effect to some undetermined change in the vasomotor mechanism, but whether the point of action is the nerve ending, the nerve fiber, or nerve cell was undetermined. He inclined to the view, however, that the reaction is peripheral. That it is to some

extent upon the nerve cells is indicated by results previously reported by Beifeld, Wheelon, and Lovelette. These investigators found that the vasomotor reaction to nicotin in dogs was strikingly augmented following the intravenous administration of saline extracts of the pancreas or the salivary glands. That this was not a foreign protein reaction was shown by the fact that the augmentation could be obtained when the animal's own glands were used. It was shown by Hoskins and Ranson that nicotin stimulates the vasomotor system partly at the sympathetic ganglia and partly in the central nervous system. Which of these possible loci was affected by the tissue extracts, Beifeld and his collaborators did not determine.

Collip(*b*) (1920) has investigated also the effect of various tissue extracts upon the depressor reaction to epinephrin. Dogs and rabbits served as experimental animals. These were anesthetized with ether. Extracts were made from thyroid, pancreas, thymus, corpus luteum, hypophysis, testes, and parathyroid glands. Sometimes commercial desiccated material was used, at other times the fresh tissue. An appropriate quantity of epinephrin was first administered to bring about a well-marked fall in arterial pressure. The tissue extract was then administered by vein and the same quantity of epinephrin again injected. In a typical instance in a dog 3 c.c. of 1:50,000 epinephrin caused a fall of 16 mm. in arterial pressure. After the administration of 10 c.c. of thyroid gland extract a sharp fall of pressure again occurred, but the normal level was soon regained. The same quantity of epinephrin was again injected and, instead of a fall of pressure as before, a rise of 20 mm. occurred. Within a short time the effect of the tissue extract was lost and the depressor reaction to epinephrin again reappeared.

The relation of anesthetics to the reactions to epinephrin has, of course, been incidentally studied many times in connection with observations upon the pharmacology of the drug. That profound anesthesia changes the depressor to a pressor reaction has been reported by Collip, as discussed in another paragraph. If sufficiently deep the anesthesia decreases the pressor response, as reported by Rous and Wilson (1919). When the pressor response of a dog the blood-pressure of which was determined under cocain anesthesia was compared with the reaction of the same animal under moderate ether anesthesia it was found to be decreased (Berry). Subsequently, however, it was found that the cocain used as local anesthetic had augmented vasomotor irritability. When quinin and urea hydrochlorid was employed and cocain "sensitization" thereby avoided, no significant difference was noted whether the dog was etherized or not.

That change of temperature may cause reversal of the epinephrin reaction has been shown by Hartman. Having determined that a given dose of epinephrin either had no effect or else caused constriction in a limb, the structure was warmed by heat from an electric lamp. After it

had ceased dilating from the effect of the artificial heat, the quantity of epinephrin previously administered now caused a distinct dilation.

Hoskins, Rowley and Rosser studied the effects of hemorrhage upon the response to epinephrin. By the injection of nicotin it was found that the irritability of the vasomotor mechanism is increased by hemorrhage of a degree to leave the blood-pressure at the normal level. Under these conditions the reaction to epinephrin remained unchanged. With animals subjected to a greater degree of hemorrhage, however, both Bardier and Rous and Wilson found that the reaction was materially decreased. This probably indicates merely that the vasomotor mechanism was under a mechanical handicap incident to the loss of fluid. If the hemorrhage were so profound as to result in marked and prolonged asphyxia of the reacting tissues, it is to be supposed that the reaction would ultimately be decreased as the reaction of any tissue to any type of stimulation is depressed under the same condition.

Snyder and Andrus observed reversal of the reaction to epinephrin in the isolated heart of a terrapin when the hydrogen ion concentration of the solution with which it was being perfused was changed. Thus they found that epinephrin augmented the tonus evoked by a Ringer's solution of pH. 7.8, but caused a diminution of tonus when the pH. was 7.0. Snyder and Campbell found likewise that a reversal of the constrictor effect of epinephrin, when perfused through the circulation of the frog, could be brought about by changes in hydrogen ion concentration. Decreasing the acidity increased the vasoconstrictor effect and vice versa.

Gruber was unable to obtain vasodilatation in limb vessels the nerves to which had just been severed, although this was easily evoked in the normal limb. He concluded that lack of vasodilator action was due to loss of tonicity in the vascular musculature. The vasodilator reaction again appeared as the vessels regained tonicity, as they do in time after denervation.

Collip(*c*) (1921) has reported observations which perhaps explain the failure of earlier observers to note the depressor effects of epinephrin. It was noted that reversal of the depressor action could be effected in dogs merely by increasing the depth of the anesthetic. The depressor effect again returned when light anesthesia was resumed. The reversal could be brought about very quickly, particularly with ether anesthesia, though also somewhat more slowly with chloroform. By alternating between light and deep anesthesia reversal could be obtained time after time. That the reversal is not due to changes in the concentration of the anesthetic per se is indicated by the fact that the reversal appeared with striking promptness. The phenomenon could not be associated with changes of blood-pressure, reversals being easily elicited while this was maintained at a constant level. Collip also extended Snyder's observations on the relation of hydrogen ion concentration to this vasomotor reversal. It was found in

the dog that the sudden administration by vein of a fairly large dose of sodium carbonate resulted in the change of the depressor reaction to a pressor reaction. A subsequent injection of acid sodium phosphate was found to antagonize the pressor effect. This result proved to be obtainable repeatedly in the same animal.

From these data it is evident that the entire pharmacology of epinephrin demands re-investigation. The great proportion of the recorded data were obtained before there was any realization of the possibility that relatively slight changes in attendant circumstances may completely reverse the reactions obtainable.

Conclusion

In conclusion, it should again be emphasized that most of the data summarized in the foregoing discussion are of pharmacological rather than physiological significance. There is no reliable evidence that epinephrin is ever discharged from the suprarenal glands in more than minute quantities. Solutions greatly transcending in concentration those found even in the lumbo-adrenal veins have commonly been employed in experimentation.

Hartman envisages the situation as a whole in the following terms: "In the adult, epinephrin poured into the blood in small quantities causes by its peripheral effects constriction of the vessels of the skin, mucous membranes, and abdominal organs, driving the blood into the vessels supplying the skeletal muscles which are actively dilated for its reception through the effect on the sympathetic and dorsal root gangliar mechanisms. But as the quantity of epinephrin increases, the peripheral effect begins to overcome the gangliar effects in skeletal muscle, the intestinal vessels by action on the sympathetic ganglia begin to dilate and the blood is reversed in its path. Although the effect of epinephrin on blood-pressure, a fall with small doses and a rise with larger amounts, is the more evident, the differential effect is the more important."

The General Pharmacology and Toxicology of the Suprarenal Glands . . . . . *Frank A. Hartman*

Response of the Pupil to Epinephrin—Response in the Alimentary Canal—Response of Ureter, Bladder and Urethra—Response of the Genital Organs—Response of Smooth Muscle in the Skin—Response of Sweat Glands—Response of Pigment Cells—Response of Glands—Respiratory Effects—Influence of Epinephrin upon Kidney Activity—Influence on General Metabolism—Influence on Sugar Metabolism—Influence on Body Temperature—Influence on Muscular Activity—Toxic Effects of Epinephrin—Location of Epinephrin Action.

The General Pharmacology and Toxicology of the Suprarenal Glands

FRANK A. HARTMAN

BUFFALO

The isolation of epinephrin paved the way for a tremendous amount of research in physiology and pharmacology. Although much had been done in the study of suprarenal extracts, the work was necessarily more or less inaccurate because of the impossibility of measuring dosage. The study of epinephrin effects has outstripped that of any other hormone. To what precise extent these effects are physiological is at present a mooted question as we are not sure of the amounts of epinephrin which are released under physiological conditions. Therefore this must be carefully kept in mind in any description of epinephrin effects.

This hormone affects smooth muscle particularly but it does so through the sympathetic system as shown by Elliott(*b*) who, after a very comprehensive study came to the conclusion that the reaction elicited was similar to that resulting from sympathetic nerve stimulation, the extent of the reaction depending upon the frequency of normal impulses passing through the sympathetic nerves to the muscle in life. A review of the effects of epinephrin upon smooth muscle as well as other tissues of the body follows.

Response of the Pupil to Epinephrin.—Although the intravenous injection of epinephrin may cause elevation of the lid, retraction of the nictitating membrane and dilatation of the pupil, to a certain extent normally, the effects are much more pronounced after degeneration of the postganglionic fibers due to extirpation of the superior cervical ganglion. Moreover, the application of epinephrin to the conjunctiva has no effect upon the pupil (Lewandowsky(*a*)(*b*)) until after extirpation of the superior cervical ganglion when marked dilatation may result.

Ehrmann(*a*)(*c*) has employed the enucleated frog's eye immersed in isotonic NaCl solution as a test for epinephrin, this being sensitive to dilutions of 1:20 million. At one time this method served as a quantitative test for epinephrin in various animal fluids, but now it is known that many other substances give a similar reaction. Some of these are tyrosin (Pick

and Pineles) and pyrocatechin (Waterman and Boddaert). It is now known that the test has little value in urine although the denervated mammalian eye has been used more recently with considerable success as a test for epinephrin in the circulating blood by Stewart and his collaborators.

The work of Meltzer and Auer(*a*) on rabbits is particularly illuminating in respect to epinephrin dilatation of the pupil. For this reason it will be given somewhat in detail.

In normal rabbits subcutaneous injections of epinephrin produce no effect on the pupil provided the dose is not large enough to cause asphyxia. After the removal of the superior cervical ganglion it is possible to secure maximal pupil dilatation from 0.6 c.c. of 1:1,000 epinephrin injected subcutaneously.

The dilatation occurs within fifteen minutes after the injection and lasts for more than two hours. During maximum dilatation the pupil does not react to light; moreover, eserin has little effect at this time except in the normal eye.

These effects do not occur until about twenty-four hours after removal of the superior cervical ganglion. Cutting the sympathetic nerve below does not serve the same purpose. The instillation of the epinephrin into the sac before removal of the ganglion is without effect but after the excision such instillations act similarly to subcutaneous injections although the dilatation is produced with greater difficulty and does not last so long. Epinephrin produces dilatation just as effectively three and one-half months after excision of the ganglion except in the case of instillation.

Meltzer records two instances in which cats were made to drink 6 c.c. of epinephrin (presumably 1:1,000) in milk, the superior cervical ganglion having been removed some time before. He states that about an hour after the ingestion the pupil on the operated side began to dilate, although not to any great degree. The dilatation lasted for a few hours. The explanation of the phenomenon of "paradoxical" pupil dilatation which has been offered is that normally impulses are being sent from the superior cervical ganglion, which easily antagonize the effects of epinephrin absorbed from subcutaneous injections or from instillations. Removal of the ganglion eliminates this antagonism.

More recently Joseph has found that epinephrin causes relaxation of the sphincter pupillæ which has been partially or completely excised. Solutions of 1:1,000,000 or stronger cause maximal relaxation. This reaction is similar to that of the intestinal strip. He tested the sphincter from man and the lower animals.

Response in the Alimentary Canal.—Although relaxation of the intestine is usually considered the more typical effect of suprarenal extract (Ott, Bunch, Boruttau, Pal, Cannon and de la Paz), increased tonus and peristalsis has been observed (Ott, Bunch).

In spite of the effect which epinephrin may have upon the circulation, it may also affect the smooth muscle of the canal for the inhibition is not necessarily synchronous with the pallor of the intestine (Langley(*a*)).

The two effects, inhibition and stimulation, seem to depend upon the dosage of epinephrin, for it has been shown by Hoskins(*e*) (Fig. 1) that doses just below the threshold for inhibition will frequently cause an increased tonus as well as an increased rhythmical activity.

The power of inhibition in the intestine has been used as a quantitative test for epinephrin.

The response of other parts of the tract is similar to that of the intestine except that the pyloric, ileo-colic and internal anal sphincters are contracted just as though stimulated by the sympathetic nerves (Elliott(*b*)). The rabbit is an exception to this in the case of the cardiac and internal anal sphincters, epinephrin causing relaxation. In this animal epinephrin produces relaxation of the esophagus and marked inhibition of the large intestine.

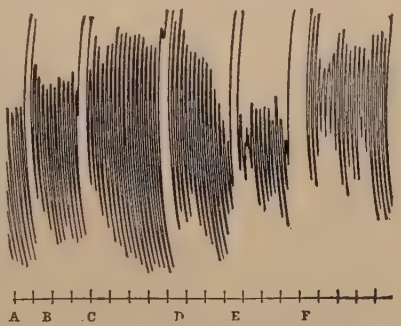

Fig. 1. One-half the original size. A segment of the small intestine of the rabbit beating in, *A*, Ringer's solution; *B*, Ringer's solution; *C*, epinephrin 1:1,000,000,000; *D*, Ringer's solution; *E*, epinephrin 1:500,000,000; *F*, Ringer's solution diluent in *C* and *E*, Ringer's solution. Time = 30 seconds. (After Hoskins, Am. J. Physiol.)

The sympathetic nerves in birds and amphibia are mainly motor in function. Here epinephrin causes constriction (Dixon), further corroborating the generalization that epinephrin, if it acts at all, produces a response identical with sympathetic stimulation. The esophagus of the frog and toad appears to differ from other parts of the alimentary canal, being inhibited by epinephrin (Boruttau). In the fowl the large intestine is relaxed while other parts of the canal are contracted. Here also stimulation of the spinal roots of the sympathetic nerves acts likewise.

Loeper and Verpy suggest that there may be digestive syndromes originating from the suprarenal. They found that the intramuscular injection of 1 mgm. of epinephrin in human subjects caused an increase in the secretion of HCl in the stomach as well as augmentation and acceleration of the contractions in the digestive tract.

Response of Ureter, Bladder and Urethra.—Intravenous injections of epinephrin cause little effect in the bladder of the dog, rabbit, rat, hedgehog and guinea pig. The effect is also slight in the monkey (rhesus), relaxation occurring to a small degree. On the other hand marked effects are produced in the cat (Lewandowsky(*b*)), goat and ferret, relaxation being produced in the first and contraction in the last two

animals. But when the motor sympathetics are paralyzed by ergotoxin, epinephrin causes relaxation of the ferret's bladder.

Epinephrin parallels the action of faradic stimulation of the hypogastrics. As an illustration Elliott(*b*) cites two abnormal cases of cats which failed to give the typical bladder response to epinephrin; likewise it was found that stimulation of the hypogastric nerves in these individuals failed to inhibit the bladder. In most cats electrical stimulation of the hypogastric nerve causes a brief contraction of the fundus of the bladder followed by marked relaxation of the bladder and a very marked contraction of the urethra.

Epinephrin increases the rate of contraction and tonicity of the ureter, more particularly the upper portion (Satani). A quiescent ureter can be revived and started to beat by the addition of one drop of 1:10,000 epinephrin in 50 c.c. of Locke's solution (Macht). After previous administration of ergotoxin epinephrin inhibits the ureteral contractions.

Response of the Genital Organs.—Inasmuch as the genital organs receive nerves from the lumbar sympathetic, response to epinephrin would be expected.

Intravenous doses of epinephrin cause contraction of the *external genital organs* the blood vessels being constricted at the same time. The *tunica dartos* of the testicle on the other hand relaxes under the same influence (Lieben(*b*)).

Epinephrin causes increased activity of the *vas deferens* (dog, guinea pig and sheep) and also increases the tone of the *prostate* (Waddell(*a*)).

It has been shown by Waddell(*b*) that freshly excised *seminal vesicles* of the rat and guinea pig undergoing rhythmic movement in isotonic salt solution increase their activity both in tone and rhythmicity under the influence of epinephrin (see Langley(*a*) also).

Both the circular and longitudinal musculatures of the *vagina* of rabbits, dogs, hogs and sheep are stimulated by epinephrin, while those of cats, rats, guinea pigs and cows are depressed. It is supposed that the motor sympathetic innervation is more powerful in the former and the inhibitory in the latter (Waddell(*d*)).

The effect of epinephrin upon the *uterus* is very striking. Biedl(*g*) says that the intravenous injection of epinephrin produces a degree of uterine anemia and a violence of contraction, not obtained through the action of any other substance. In pregnant animals, abortion was frequently caused by such injections. This substance not only stimulates the uterus to activity but increases its excitability so that physiological or artificial nervous stimuli become more effective.

Because of the marked contraction produced injections of epinephrin have been used in obstetrics to reduce the size of the uterus and at the same time to check hemorrhage (Neu). Injection into the uterus itself avoids the bad results which may arise from intravenous administration.

There are differences in the response of the uterus in different species. The rabbit's uterus whether pregnant or not is stimulated to contraction by epinephrin (Langley(*a*)). The reverse effect is produced in the uterus of the rat and guinea pig, epinephrin causing inhibition whether or not pregnancy exists. However, the uterus of the cat when pregnant is contracted and when non-pregnant is relaxed under the influence of epinephrin (Cushny(*a*), Dale).

The isolated uterus because of its great sensitivity has been used as a quantitative test for epinephrin (Fränkel). By this means dilutions of 1:20,000,000 may be detected.

Response of the Bronchioles. — Although there appears to be some uncertainty as to the action of epinephrin on the bronchioles there are numerous clinical observations that it relieves the spasm of bronchial asthma (Kaplan, Jagic). It seems that when the bronchioles are in a condition of tonic contraction epinephrin will cause considerable dilatation. Dixon and Ransom found that when the bronchioles were not fully relaxed epinephrin dilated them to the maximum. However, Golla and Symes have usually obtained constriction of the bronchioles from epinephrin unless constriction had previously been established by some other drug. They suggest that the usual action is constriction while the use of some drug which previously constricted reversed the action. In rebuttal the experiment of Dixon and Ransom may be cited in which they obtained epinephrin dilatation of the bronchioles after constriction of the latter through vagus stimulation (Fig. 2). This would indicate that the state of contraction of the muscle is the determining factor.

Fig. 2. Lung volume above, blood-pressure below. Urethane anesthesia. *A*, Accelerator bundle stimulated by faradic current; *B*, Electrical stimulation of vagus; *C*, Injection of 1.0 c.c., 1:10,000 epinephrin. Time = 5 seconds. (After Dixon and Ransom, Am. Jour. Physiol.)

Paralysis of the constrictors by ergotoxin enables epinephrin to produce dilatation of the bronchioles with greater ease. Jackson(*b*)(*d*)(*e*), however, found that ergotoxin possessed no very marked specific action on the bronchioles. The negative results of many investigators may be due to

the fact that the anesthetic employed frequently maintains the bronchioles in a more or less dilated condition. Then if epinephrin produces any effect it is most often constriction. The evidence at present appears to favor the view that this substance will produce dilatation of constricted bronchioles. At any rate bronchial asthmatic spasm is said to be relieved by the subcutaneous injection of epinephrin (Jagic).

Response of Smooth Muscle in the Skin.—Usually smooth muscle that is easily contracted through sympathetic stimulation is likewise readily affected by epinephrin. The smooth muscle of hairs proves to be an exception. Here the response to sympathetic stimulation may be very marked while epinephrin may have but slight effect in some animals while in others the two effects run parallel. Elliott(*b*) suggests that the response to epinephrin depends upon the extent to which the structures are commonly used, rather than upon the sympathetic irritability.

The variable response to epinephrin injections in the *arrectores pilorum* of different animals is one of the best illustrations of this dependence of the reaction upon the varying functional use of the structure by each animal. Elliott has observed that the hairs on the back of the domestic cat are not easily affected by epinephrin (sympathetic stimulation easily erects the hairs) while those on the scruff of the neck and down the middle of the back on a fox-terrier are readily affected. The hairs on the tail of the mongoose are erected with great ease by epinephrin. The domestic cat does not exercise the function of the *arrectores pilorum* to any great extent while in the terrier the practice is more common and the mongoose is said to fluff its tail with every fleeting emotion.

Birds illustrate the same generalization. Their feathers possess a sympathetic innervation, but those birds which frequently erect their feathers have the latter most easily moved by epinephrin. Thus the cock's feathers readily respond while the hen's feathers are affected with some difficulty.

Response of Sweat Glands.—Langley(*a*) was unable to induce sweat secretion in the cat's paw either by intravenous or local subcutaneous injections of epinephrin in spite of the fact that the sweat glands are supplied by sympathetic fibers. Elliott tried to stimulate the sweat glands in the human hand but a decrease in the secretion resulted, due probably to the anemia produced.

Dieden has been able to produce sweating of the cat's paw by the injection of epinephrin into the pad of the foot but only after section of the sciatic nerve or else during deep anesthesia. Intravenous injections or subcutaneous injections in other regions were ineffective.

Response of Pigment Cells.—An agglomeration of the pigment granules in the retina of the frog due to epinephrin has been described by Klett. This may occur even in the presence of light, which ordinarily causes migration of the granules.

Arey and Bigney describe this change as an expansion of the pigment cells.

The pigment cells of the frog's skin on the other hand are constricted by epinephrin. This appears to be an effect similar to that caused in the horned toad as it is due neither to anemia nor to a reflex (Lieben(*a*)).

The melanophore reaction of the horned toad has been carefully worked out by Redfield(*b*). He found that nervous excitement causes contraction of the melanophores. This reaction is prevented in any area by a blocking of the circulation or by removal of the suprarenals but not by severing nervous connection.

Response of Glands.—Epinephrin stimulates secretion of the salivary and lachrymal glands (Langley(*a*)). Denervation of the submaxillary gland by cutting the chorda tympani and destroying the superior cervical ganglion does not interfere with the reaction, therefore the point of stimulation must be peripheral. Constriction of many seconds' duration precedes the dilatation which accompanies the secretion (Biedl(*g*)). Atropin in very large doses inhibits the secretion.

Large doses of epinephrin excite secretion of the mucous glands of the mouth, esophagus and trachea. A rise in blood pressure precedes the secretion, which quickly reaches a maximum and gradually subsides (Biedl).

Langley says that epinephrin increases the output of a secreting pancreas but has little or no effect upon a quiescent organ. Mann and McLachlin say that this hormone decreases pancreatic flow when any effect is produced, even with doses which cause a fall in blood pressure.

It is claimed that gastric secretion is also stimulated by epinephrin (Yukawa).

Respiratory Effects.—Oliver and Schäfer were the first to notice that suprarenal extract causes either an arrest or a decrease in the amplitude of the respirations. As shown later this was due to epinephrin. A first injection causes a prolonged expiration which extends into a state of apnea more or less persistent. The apnea is obtained more easily in anesthetized than in conscious animals. Repeated injections of epinephrin at sufficiently short intervals produce an action on the respiratory rhythm which becomes less and less marked although the blood pressure response may not change (Langley(*a*), Langlois and Garrelon). The decrease in the respiratory effect is greater in an excess of oxygen. Section of the vagus diminishes the duration of the apnea but does not suppress it.

Of perhaps greater interest is the effect of physiological doses of epinephrin. All of the earlier workers used large doses, far above anything physiological. Nice, Rock, and Courtright using the contractions of the diaphragm to indicate respiratory change made a study of this problem. They found that depressor doses as well as pressor doses up to a certain point cause an increase in the depth of the respiration, the in-

creased depth being in proportion to the dose within certain limits. The augmentation might be as much as 35 per cent (Fig. 3). Doses of 0.3 c.c. or more of a 1:1,000 solution produce in a cat the opposite effect, viz., a reduction in the amplitude of the breathing. Here the decrease within certain limits is in direct proportion to the dose. These effects occur whether the blood pressure be high or low and also regardless of whether the vagus nerves are cut or not. When the breathing was irregular in some animals epinephrin (small doses) made it regular.

These authors were inclined to interpret the effect as due to a stimulation of the nervous center for they were unable to obtain any increase in the contraction of isolated strips of diaphragm when stimulated electrically in the presence of epinephrin in a bath. Moreover, it has been shown by perfusion of the medulla (Brown) that epinephrin acts directly on the respiratory center, small doses causing increase in depth and rate of respiration while large doses diminish the depth and rate or may even stop it.

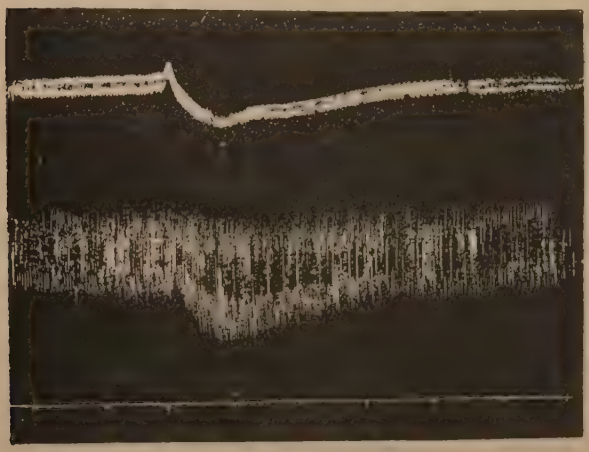

Fig. 3. Cat. Blood-pressure above, record of diaphragm contraction below. Augmentation of contraction by a depressor dose of epinephrin (0.35 c.c., 1:50,000). (After Nice, Rock and Courtright, Am. J. Physiol.)

We have found this respiratory effect to occur in man after the injection of epinephrin. The intravenous administration of 1.0 c.c., 1:50,000 dilution in a conscious subject caused an increase in the respiratory rate from 24 per minute before, to 42 per minute after, while amplitude was also increased. These changes lasted for 90 seconds. The effect was not the result of suggestion because injections of distilled water were given at times instead of epinephrin, the subject being kept in ignorance of the kind of injection by use of these controls. However, this subject was unusually sensitive because three others receiving similar doses of epinephrin showed no changes in respiration except in one instance in which there was a small increase in amplitude.

Influence of Epinephrin upon Kidney Activity.—That epinephrin may exercise an important influence upon kidney activity is indicated by the work of Cow and others. Cow demonstrated in the cat that there is direct vascular connection between the suprarenal and the kidney. This consists of a fine rete of vessels embedded in the perirenal fat and join-

ing the suprarenal medulla with the kidney (Fig. 4). When injected by way of the rete, these regions appear where the vessels enter as cones with their bases in the renal capsule, their apices extending into the renal medulla in many instances. Cow was led to this discovery by the observation that when the kidney was perfused by fluid entering through the thoracic aorta, all visible arteries except the renals being tied, the amount of urine progressively decreased as did also the rate of the perfusion flow. On the other hand perfusion directly through the renal artery invariably caused a progressive rise in the amount of urine, usually although not always accompanied by an increase in the perfusion flow. The different results in the two methods of perfusion could be accounted for by passage of a portion of the perfusion fluid through minute vessels, which had been overlooked, leading to the suprarenal from whence epinephrin was washed and carried to the kidney.

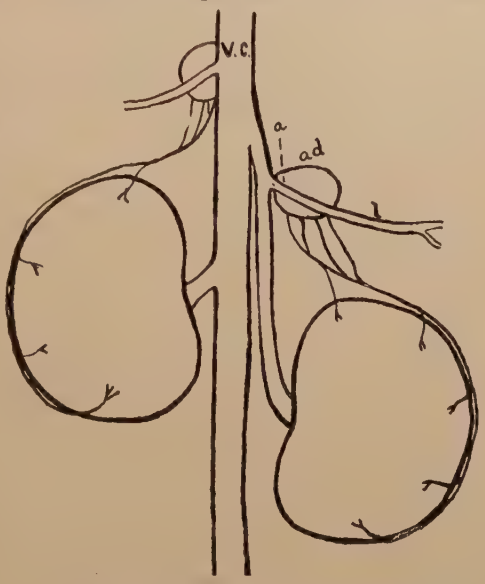

Fig. 4. Veins to the suprarenal of the cat. The rete of vessels connecting the suprarenal with the kidney, after the diagram of Cow. *ad.*, suprarenal; *a.*, common lumbo-suprarenal vein; *l.*, lumbar vein joining the suprarenal vein; *v. c.*, vena cava.

Whether such vascular connection between the suprarenal and kidney exists in man has not been shown so far as we know. The work of Marshall and Kolls indicates its absence in the dog. However, suprarenal products might affect the kidney by way of the general circulation as shown by Addis and his coworkers.

Instead of a reduction of the excretory power of the kidney as indicated by Cow's perfusion experiments (urine volume determined) Addis, Barnett and Shevky found that suitable doses of epinephrin injected subcutaneously produce an increase in the urea secretion (rabbit) when measured over hourly periods. There is a certain amount of epinephrin which produces the greatest increase in function, smaller amounts having less and less effect until there is no change from the normal. With larger amounts the augmenting effect on secretion also becomes less until, with relatively large doses, a decrease in function is found.

Intravenous doses of epinephrin, at least in the amounts which cause a visible change of the volume of urine, inhibit the urine flow for a brief interval as shown by Gunning. Although he did not observe diuresis fol-

lowing, it would be well to base our conclusions upon urine flow over long periods of time as Addis did. Moreover, the determination of some constituent is highly important.

Wels has shown that the injection of 1 mgm. of epinephrin in the human subject diminishes diuresis and also reduces the excretion of NaCl.

The reduction of urine flow as observed in Cow's perfusion experiments might well be due to massive doses of epinephrin being washed into the kidney (this is indicated by the decrease in perfusion flow) whereas in the normal animal the physiological amounts of epinephrin reaching the kidney either directly or indirectly might be of the same magnitude as those by the subcutaneous injections of Addis and his coworkers.

Marshall and Davis have shown quite clearly that the excretory power of the kidney is very much reduced (see p. 330) in animals from which the suprarenals have been removed. The fact that this occurs with a normal blood pressure and while the animal is in excellent physical condition indicates that the suprarenals play an important part in renal activity.

Bevier and Shevky have also shown that removal of the suprarenals in rabbits decreases the excretion of urea.

Influence on General Metabolism.—The effect of epinephrin on metabolism in its normal physiological amounts is not known. Just how far suprarenal insufficiency is due to epinephrin insufficiency we cannot say. Some believe that epinephrin is not necessary in the organism. However, the influence of epinephrin upon kidney activity and upon the prevention of muscular fatigue indicates that this substance may exercise a definite function normally.

Most of our information concerning the influence of epinephrin upon metabolism is based upon the results from huge doses, amounts far beyond anything occurring in physiological secretion. Therefore in a discussion of the metabolic effects it must always be kept in mind that the effects may quite easily be abnormal. It is known that very large doses of epinephrin often produce the opposite effect to that from small and more nearly physiological doses, e. g., upon kidney secretion.

Some authors have been unable to find any change in the metabolism of nitrogen after subcutaneous or intravenous injection of epinephrin into healthy animals (Quest). According to Underhill and Closson epinephrin produces an increase in the excretion of nitrogen in starving animals. Eppinger, Falta and Rudinger found an increase in the metabolism of protein and fats in such animals, this being attributed to an improvement in the thyroid function.

Sandiford has obtained an increase in the metabolic rate from the subcutaneous injection of 0.5 c.c. of 1:1,000 adrenalin in man.

Influence on Sugar Metabolism.—Blum(*a*) appears to have first discovered that glycosuria is produced from subcutaneous or intravenous in-

jections of suprarenal extract. This was observed in animals deprived of carbohydrates as well as those which were starving. Very soon after this, Herter found that the injection of epinephrin into the peritoneal cavity produced marked glycosuria. He believed this was due to action on the pancreas because painting the latter produced glycosuria while the injection of epinephrin into the liver had less effect.

Paton(*a*) believed that this condition was a true diabetes for it occurred after the stored carbohydrates had been removed from the body by phloridzin. Moreover, he found that there were disturbances in the distribution of nitrogen in the urine similar to those occurring in diabetes. On the other hand Underhill and Closson were unable to find any alteration in the distribution of nitrogen from subcutaneous injections of epinephrin.

Paton(*b*) has used ducks and geese in an attempt to show whether the pancreas is involved in epinephrin glycosuria. V. Mering and Minkowski had already proven that removal of the pancreas in these birds did not cause diabetes. Paton found that he could produce glycosuria by the injection of epinephrin after removal of the pancreas. He concluded that epinephrin does not act through the pancreas.

It has been suggested by Underhill and Closson that the mechanism of epinephrin glycosuria is of nervous origin, acting through the sympathetic system. This action is due to a stimulation of the organs storing glycogen causing a release or preventing storage or both, hyperglycemia and glycosuria resulting. Achard, Ribot and Binet have performed experiments on dogs which support the idea that epinephrin prevents the storage of sugar. They found that the simultaneous injections of sugar and epinephrin produced a greater hyperglycemia than the sum of the increases obtained from the injection of like quantities of the two substances at different times. The duration of the hyperglycemia was also prolonged. Fresh pancreas extract added to the glucose-epinephrin mixture reduced the hyperglycemia.

Epinephrin glycosuria is due to hyperglycemia great enough to cause sugar overflow through the kidney. At first it seems that excess sugar escapes from the kidney more easily, while with succeeding doses the escape becomes more difficult and may not occur at all. This does not appear to be due to a decrease in the amount of sugar in the blood but more to an increased power of the kidney to block the exit of sugar (Pollak(*a*)). When glycosuria appears it is said to last only as long as there is epinephrin in the blood (Ritzmann). A continuous injection of epinephrin diluted 1:2 million may not produce glycosuria when injected at the rate of 1 c.c. per minute, but a velocity of 3 to 4 c.c. per minute may be sufficient to do so. There is a long latent period due perhaps to the time required for the transformation of the glycogen to sugar. The amount of sugar released is said to be in proportion to the amount of epinephrin available per unit of time, this being the case only within a certain range. However, the

effect of the epinephrin is greater when large amounts of glycogen are stored. If there is but a scanty glycogen storage larger doses of epinephrin are required to bring about a given result.

Ritzmann has shown that intravenous are more effective than subcutaneous injections. This is true when the epinephrin is infused over a period of time. As much as 80 per cent of the epinephrin injected subcutaneously appears to be without effect judging from the fact that it required five times as much epinephrin subcutaneously to cause the excretion of the same amount of sugar as that obtained from intravenous administration. Much of the epinephrin must have been destroyed before it reached the circulation.

Small doses of epinephrin may cause no measurable depreciation in the amount of glycogen in the liver in well nourished animals. Only when toxic doses are employed can these changes be brought about (Drummond and Paton). Glycogen may disappear from both the muscles and liver if a large amount of epinephrin is used (Agadschanianz). Pollak found that levulose-glycogen was more resistant to epinephrin than was glucose-glycogen. Pentose mobilization is also resistant to epinephrin. Cosentino has been unable to produce pentosuria from injection of the latter.

Pheeas has been able to obtain epinephrin glycosuria in rabbits deprived of their glycogen by fasting. He suggests as an explanation of this, the action of hepatic diastases upon substances other than glycogen (lipoids, glycoproteins) resulting in the formation of glucose. It is assumed that epinephrin increases the hepatic diastases. As an indication that the glucose came from a larger molecule he found a notable increase in the excretion of urea and phosphates after epinephrin injection. However these would not necessarily be residues of the molecules from which the glucose might be formed.

Blum(*a*) has suggested that the glycosuria resulting from Bernard's puncture is due to a release of epinephrin through stimulation of the splanchnic nerves. Mayer(*b*) failed to obtain glycosuria from diabetic puncture after the suprarenals were removed. In addition Waterman and Smit have found an increase in the output of epinephrin after puncture of the fourth ventricle.

Kahn(*f*) has concluded that through the action of the splanchnic nerve sugar puncture makes the liver cells more sensitive to epinephrin action and also stimulates epinephrin secretion. Due to an increased sensitiveness of the glycogenolytic mechanism of the liver sugar may be released even in the absence of the suprarenals, although the sugar release is much more marked in their presence.

The pancreas opposes the action of epinephrin in the mobilization of sugar as shown by Achard, Ribot and Binet and also by the following experiments. If the pancreas has been removed in dogs either puncture of the fourth ventricle or injection of epinephrin produces both hyper-

glycemia and glycosuria which are more marked than would be the case with an intact pancreas.

On the other side of the question there is evidence that many of these hyperglycemias are more or less independent of epinephrin. Stewart and Rogoff(*g*)(*k*) have shown that the hyperglycemias of asphyxia and ether anesthesia can occur without any detectable liberation of epinephrin. Animals were employed from which both suprarenals had been removed (rabbits) or from which one gland had been removed and the nerves to the other cut (cats). A sufficient time was allowed to elapse so that complete recovery from the operation might take place and the liver might accumulate glycogen.

Hyperglycemia could be produced in these animals by asphyxia, ether anesthesia and piqûre. No epinephrin could be detected in the circulation by methods which are sensitive to one six hundredths of the normal output from intact glands (rabbit's intestine and denervated eye reactions).

These experiments seem to prove that the suprarenals are not essential for hyperglycogenolysis. Macleod and Pearce(*a*) had previously concluded that the suprarenal glands play an important part in the control of glycogenolysis for it had been found that only when the suprarenals were intact did stimulation of the nerves to the liver cause hyperglycogenolysis. When the suprarenals had been removed such stimulation was without effect. Tying the main suprarenal veins usually produced a similar result. On the other hand these authors found that after complete section of the hepatic plexus, splanchnic stimulation only occasionally produced hyperglycemia although injections of epinephrin when the hepatic plexus was cut caused hyperglycemia.

In conclusion we may say that epinephrin does not appear to be essential to the production of the hyperglycemias of asphyxia, ether and piqûre and perhaps other causes. On the other hand epinephrin does stimulate glycogenolysis and may assist in the glycogenolysis produced by other means. (See Keeton and Ross and also Kahn(*f*).)

Influence on Body Temperature.—Injections of epinephrin which are slowly absorbed may produce a rise in temperature. Thus subcutaneous and intraperitoneal injections are more effective than intravenous injections (Biedl(*g*)). The cause of the increased temperature is due, at least in part, to the increased heat production (Lusk and Riche; Tompkins, Sturgis and Wearn).

Sandiford has found that an injection of 0.5 c.c. of 1:1,000 adrenalin chlorid injected subcutaneously in the human subject causes an increase in the metabolic rate, the maximum usually occurring within ten to thirty minutes after the injection and lasting from one and one-half to two hours. This increase was usually accompanied by increased pulmonary ventilation. There is a similarity of the metabolic rate curve following epinephrin injection to that found by Lusk in carbohydrate plethora.

Influence on Muscular Activity.—A number of observations point to a close relationship between the suprarenals and muscular activity. First of all the muscular weakness of suprarenal insufficiency suggests an intimacy between the two tissues.

After intense prolonged muscular activity the vacuolization of the suprarenals (Bernard and Bigart, Bardier and Bonne) and the disappearance of the lipoid-cholesterol bodies from the cortex (Laignel-Lavastine) indicate exhaustion of these glands.

Furthermore, Elliott and Tuckett have found that the size of the suprarenals increases with the development of the muscles. In this connection the observations of Watson(*b*) are very important. He noticed a marked difference between wild and tame rats in the percentage of the suprarenal to body weight. The average percentage weight for young tame rats was found to be 0.035 while that for young wild rats of similar weight 0.066. The difference is even greater in adults, the percentage weight averaging 0.019 for tame animals and 0.052 for wild. It should be noticed also that the percentage weight decreases much less in wild than in tame rats as the animals mature. This suggests that as the tame rat reaches full growth the need for suprarenal tissues decreases because the growth processes are reduced and no great muscular activity demands suprarenal function. On the other hand in the wild rat although growth processes are reduced at maturity, the extremely active muscles require great function of the suprarenals.

Watson kept a series of wild rats in captivity for 10 weeks. At the end of that time the average percentage weight of the suprarenals was 0.038. They were fed bread and milk. The decreased activity would seem to account for this unless it were due to a change in diet.

Just what part the suprarenals might play in muscular activity is uncertain but there is evidence that epinephrin may be of importance in muscular fatigue. The quantity of epinephrin in the suprarenals is very much decreased by great muscular fatigue (Batelli and Boatta, Carl). This has peculiar significance when connected with the observation that epinephrin delays the onset of fatigue in skeletal muscle, which has been demonstrated by Panella, Cannon and Nice, and Gruber.

Whether this beneficial effect is due to an increase in the circulation in skeletal muscle (Hoskins, Gunning and Berry) or to some other influence, Gruber's work would indicate that the effect is not wholly circulatory, for after denervation of the muscle while the vessels are in a dilated state, epinephrin benefits the fatigued muscles without an accompanying dilatation; in fact the circulation may decrease. It has been suggested that epinephrin neutralizes or destroys the fatigue products. Carnot and Josserand found that a dose of epinephrin which caused a rise of 10 cm. (Hg) in the blood pressure when injected into the femoral artery of a resting leg produced a rise of only 1.5 cm. when injected into

the femoral artery of the opposite leg after it was fatigued by tetanization. Gruber has shown that epinephrin will overcome the effects of fatigue produced artificially by injection of lactic acid and phosphates. Indeed, Gruber and Fellows have been able to restore the irritability of nerve-muscle in animals which have been dead from one to three hours (Fig. 5).

Toxic Effects of Epinephrin.—Foà and Pellacani appear to have been the first to observe toxic effects from suprarenal extracts. Intravenous injection produced dyspnea, agitation and more rapid heart rate, to be followed later by a slowing of the rate. The temperature rose to

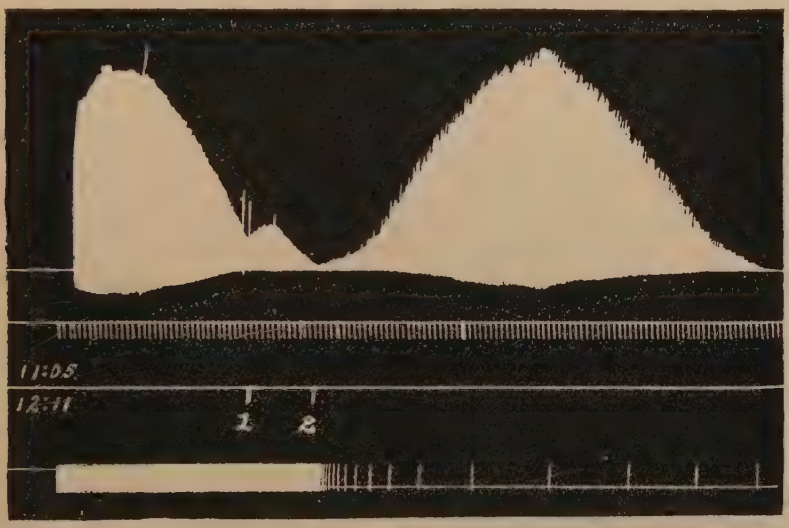

Fig. 5. Records of a muscle in a cat dead one hour. Upper, muscular contraction, time record just below (5 sec.) Lowest, rate of perfusion. 1, Epinephrin 1 c.c., 1:100,000; 2, Epinephrin 0.5 c.c., 1:1,000. (After Gruber, Endocrin.)

41.2°C, but gradually returned. Great prostration ensued. Death followed within a few hours after the injection.

Oliver and Schäfer have shown that the paralysis produced from suprarenal extract is central because stimulation of the nerve muscle preparation elicits a normal contraction after apparent paralysis.

Large doses of epinephrin (suprarenal extract, Vincent(*a*)) frequently cause bleeding from the mouth and nostrils, also hematuria, probably due to rupture of capillaries as a result of high blood pressure. Elliott(*b*) makes the statement that epinephrin produces hemorrhages in the cortex of the suprarenal sooner than elsewhere. The harmful effects of large doses of epinephrin may be due to excessive blood pressure and to a direct toxic action. The changes in the kidney of an animal which has died from epinephrin injection are striking but variable. These may be anything from simple congestion to parenchymatous nephritis with desquamation of the cells of the tubules (Drummond). Such changes may

result in death from a single dose or from several doses given at intervals. Frequently the liver shows patches of necrosis although the liver changes are so inconstant that some cases show no definite change in this organ.

The glycogen content of the liver may or may not be affected. In chronic poisoning it is not necessarily changed while in acute poisoning the glycogen is diminished if the animal lives long enough after the injection (Drummond and Paton).

Convulsions are frequent in animals before death from epinephrin. These may be asphyxial in nature as a result of acute edema of the lungs (Batelli(*e*)). The congestion may be intense and even hemorrhagic in character.

Daily injections of epinephrin even in comparatively moderate amounts in time cause atheroma of the aorta and coronary arteries (Loeper(*b*)) although this is said not to be the case in young animals (Pic and Bonnamour).

Whether significant or not it is interesting to note that the guinea pig has great resistance to epinephrin so that large doses are required to produce death. Likewise the guinea pig has a larger cortex in proportion to its size than has any other animal.

The lethal dose of natural levo-epinephrin is much less than that for dextro-epinephrin (Schultz, Abderhalden and Slavu). Likewise the former possesses a greater physiological activity.

A much greater amount of epinephrin is required subcutaneously than intravenously to produce death. When given by the mouth great quantities are tolerated. No doubt a large portion of such a dose is destroyed before it reaches the circulation (Falta(*a*)).

Location of Epinephrin Action.—It seems that epinephrin produces its effect only through mediation of the nervous system or its closely associated structures, especially through the sympathetic portion. Tissues without sympathetic innervation are unaffected by it, therefore we conclude that it has no direct action on muscles.

Myoneural Junctions. Dixon was able to paralyze the structures through which epinephrin acts upon the blood vessels by means of apocodein. The smooth muscle itself was still irritable to barium chlorid. Apocodein, at least in moderate doses, does not paralyze every epinephrin-sensitive tissue in the body. The epinephrin-sensitive tissue of the bladder is such an exception. The effect of apocodein must be a true paralysis rather than a chemical antagonism for if it were the latter all epinephrin-sensitive tissues of the body should be affected equally. Moreover, stimulation of vasoconstrictor fibers paralyzed with apocodein is without effect.

Brodie and Dixon have shown that the excitability of the vasconstrictor nerve trunks to electrical stimulation is lost within two to three hours after death, but that the reaction to epinephrin persists a few

hours later than this. They found that good epinephrin reactions could be obtained in limbs denervated two and three months before. They concluded therefore that epinephrin must act upon nerve endings which are considered to be connecting links between nerve and muscle rather than merely fine branches of nerve fibers purely nervous in structure. In others words this connecting link which they call the neuromuscular junction (myoneural junction, Elliott) does not degenerate following section of the nerve.

The two antagonistic sets of fibers in the sympathetic connect with myoneural junctions which are sensitive to epinephrin. Thus, in turn, the vasoconstrictors and vasodilators to the same part may be brought into action by the use of epinephrin (see effect of epinephrin on the circulation). The response of the vasconstrictor myoneural junctions is easily demonstrated in a perfused organ or in isolated vessels. Vasodilator myoneural junctions can be similarly demonstrated in a perfused organ and also in a part to which the nerves have been cut. However, in the last instance either the part must be perfused or else a few days must elapse after denervation in order to bring out the dilator response (Figs. 6 and 7).

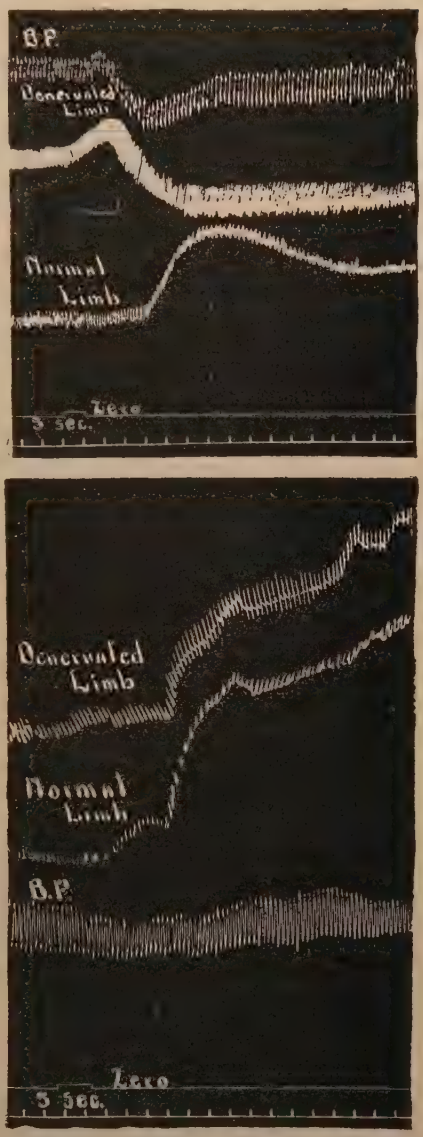

Fig. 6. Reversal of the epinephrin response in a freshly denervated limb by perfusion. Upper record—circulation to limbs intact, 1.0 c.c. epinephrin, 1:10,000 injected into the jugular vein. Lower record—limbs perfused, 2.0 c.c. epinephrin, 1:10,000 injected into the perfusion fluid. Dog 24 kgm. (Reduced one-half.) (After Hartman, Kilborn and Fraser, Amer. Journ. Physiol.)

Gangliar Mechanism. It has been shown by Hartman and Fraser that the action of epinephrin is not limited to the myoneural junction. By perfusing the limb or the intestinal loop in which the nerves are intact but in which all connection with the blood stream is cut off, dilatation can be obtained from the injection of epinephrin into the jugular vein.

Epinephrin acts upon certain structures in the sympathetic ganglia and the dorsal root ganglia (Hartman, Kilborn and Fraser(*a*)(*b*)). This has been shown by the direct application of epinephrin to the ganglia and

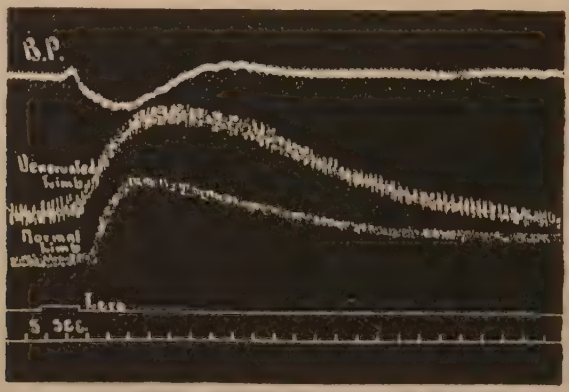

Fig. 7. Dilatation of the hind limb of a dog (14 kgm.) due to 0.8 c.c. epinephrin, 1:50,000, twenty-two days after denervation. (Reduced one-half.) (After Hartman, Kilborn and Fraser, Am. J. Physiol.)

also by perfusion of the organ in question after cutting it off from the body circulation, but avoiding injury to the nerve fibers, and then after severing the central nervous connection with the ganglia, injecting epinephrin into the circulation. When the sympathetic ganglia are being investigated

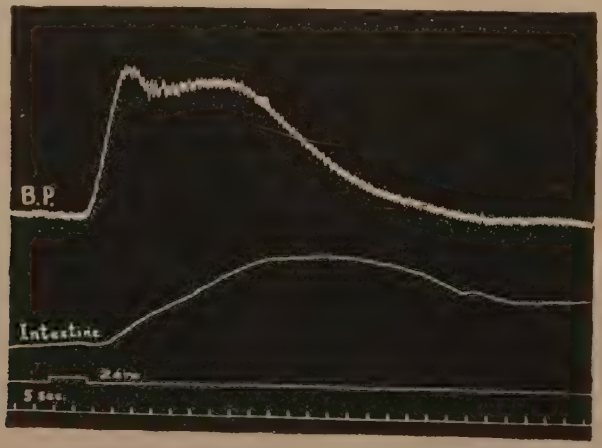

Fig. 8. Dilatation of a perfused loop of intestine of a dog (weight 13.5 kgm.) caused by the injection of 2 c.c., 1:10,000 epinephrin into the jugular vein. Postganglionic fibers intact but all preganglionic fibers cut. (After Hartman, Kilborn and Fraser, Am. J. Physiol.)

the dorsal root ganglia are destroyed while if the latter are under investigation the former are destroyed. The usual gangliar response is dilatation (Fig. 8) although occasionally constriction can be caused under certain conditions (Hartman, Kilborn and Fraser(*c*), Fig. 9).

Epinephrin also produces an action upon the medullary centers. The medulla of dogs was perfused by a mixture of defibrinated blood and Ringer's solution entering the carotid and vertebral arteries (Brown). In a majority of cases epinephrin introduced into the perfusion mixture caused a slowing of the heart and a fall in blood pressure. It seems to act directly on the vagus center because the slowing was immediate and was not connected with a rise in blood pressure. Occasionally there was a fall of blood pressure without the heart effect.

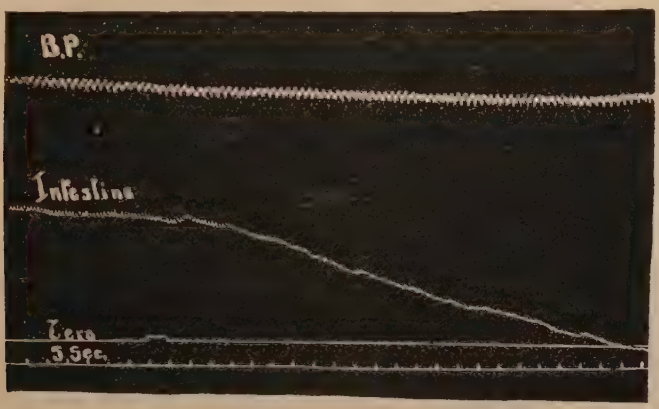

Fig. 9. Constriction of the intestine from direct application of 1:1,000 epinephrin to the superior mesenteric ganglion. Dog. (After Hartman, Kilborn and Fraser, Am. J. Physiol.)

McGuigan and Hyatt have postulated a central locus for a part of the response to epinephrin on the ground that pithing the brain prevents the secondary rise of pressure following its injection.

The respiratory center seemed to be affected also. Small doses of epinephrin often increased both the depth and rate of respiration, while large doses usually diminished the depth or rate or might even stop it.

In conclusion we may say that epinephrin can act on myoneural junctions, sympathetic and dorsal root ganglia and centers in the central nervous system, though the greater part of the effect is due to action on the peripheral neurocellular junctions.

The Pathological Anatomy and Histology of the Adrenal Glands . . . . . *J. J. Mackenzie*

Introduction—Postmortem Alterations—Congenital Anomalies—Pathological Chances in the Suprarenals as a Result of Infections and Intoxications—Suprarenal Pathology in Addison's Disease—Tumors of the Suprarenals—The Pathology of the Suprarenals in Its Relationship to Other Endocrin Glands.

The Pathological Anatomy and Histology of the Suprarenal Glands

J. J. MACKENZIE

TORONTO

Introduction

A proper conception of the pathological anatomy and histology of the suprarenal glands is difficult at the present time, on account of the lack of precise knowledge of their normal physiology. The discovery of epinephrin, the ease with which it can be demonstrated in the suprarenal medulla, in the other chromaphil tissues and in the blood, and the readiness with which pure preparations can be used in experimental investigation, has tended to give undue prominence to the epinephrin function of the glands in contrast to the more bulky and possibly more important function of the cortical portion. If we add to these difficulties the evident, but as yet quite unravelled, relationships of the suprarenals to the other endocrin organs, a relationship which has been clouded in a mist of theories, we see that the time has not yet come for final elucidation of suprarenal pathology.

In the past few years an enormous literature has grown up on the subject of suprarenal insufficiency. But in the last analysis it is questionable whether the great mass of it is worth the paper and ink expended upon it. The isolation of epinephrin and the demonstration of its pressor effect have been the grounds upon which has been built up a mountain of theory. Suprarenal insufficiency, meaning usually by that deficiency of epinephrin production, has been called in to explain not only death in acute infections but even such conditions as surgical shock. It was probably natural that this should be so, but it would be well if physicians, and especially therapeutists, would wait until the physiology of the suprarenal and the significance of the secretion of its medulla has been elucidated as fully as possible before building up beautiful hypotheses in regard to the causation and treatment of disease. The work of American physiologists in the past few years has done much to clear

up suprarenal function and not the least striking feature of this is the more precise indication of the rôle of the medullary secretion in the normal body. But these precise results of physiology lend very little support to those who would view every case of death with asthenia and falling blood pressure as due to suprarenal exhaustion.

In spite of this, however, the last ten years have produced a mass of observations upon the pathology of the glands and we are beginning to see evidence of definite association between changes in the normal contents of the cortex and medulla and certain general pathological states of the body.

Post-mortem Alterations.—Post-mortem changes are fairly common in the suprarenal glands. As a rule the zona reticulata, or inner layer of the cortex, is the area which shows this most frequently. The change in its earliest manifestation consists in a separation of the cells from one another and a failure of the nucleus to take the nuclear stain. A more advanced state is seen in an autolytic softening of the inner cortical zone. As a result of this softening of the reticulata, the outer cortex may be completely separated from the medulla and the central part of the gland converted into a cavity filled with brownish or hemorrhagic débris. It was this change, noted by several observers in the seventeenth century, which led Thomas Bartholinus to describe the organs as "capsulæ atrabiliariæ" (Literature in Biedl(*c*) Janus, 1910, p. 193). The great majority of pathologists have felt convinced that this condition was purely a post-mortem change and it is so described in all the leading text-books. The greatest possible variation exists in the degree of softening. The relationship of the external temperature and the number of hours which have elapsed since death also shows great variation, so that one cannot say positively that in delayed necropsies and at high summer temperature one will always find softening. At the same time it is more apt to follow deaths from acute infection or conditions where there is congestion and edema of the inner portion of the gland. In a recent paper Materna has returned to a consideration of the question and as a result of his studies he argues that slight degrees of softening or cavity formation are relatively common and are at least agonal in their origin. But he also cites cases in which he thinks that he has been able to demonstrate reparative changes which would indicate an origin some considerable time before the death of the patient. He does not entirely deny the occurrence of post-mortem softening but argues for a more frequent development of the condition before death. In spite of Materna's arguments, however, the general experience of pathologists would lead them to regard the extreme softening, which caused observers of the seventeenth century to describe the organs as capsules enclosing a black fluid, as due to post-mortem autolysis. Rough handling of the glands before fixation may increase or aggravate the amount of breaking down of the medulla. This is especially liable

to occur in the reticulata, which is a less resistant layer lying between the firmer fasciculata and the more fibrous medulla. At the same time, the reticulata is especially liable to show before death the effects of toxic substances and it may be that the more frequent occurrence of softening in acute infections may have a basis in ante-mortem disintegration of the reticular cells.

Congenital Anomalies.—Congenital anomalies of the suprarenals consist in aplasia, hypoplasia, or various types of dystopias. A complete absence of suprarenals is hardly conceivable, yet cases are reported in the literature of such a condition. Where this total aplasia occurs in non-viable monsters, especially those with extensive cerebral defects, the evidence is conclusive, and cases are cited by authors whose attention was especially directed to the suprarenals and who would not be likely to miss them. But the reported absence of suprarenals in subjects who have lived for a longer or shorter period after birth must be regarded as due to faulty observation. It is certainly significant that cases of total absence of suprarenals in adults are more common in the early literature. One case, which is frequently cited, was reported in 1856 by Martini. This was in a man forty years of age, married, with two children. The patient died of pulmonary tuberculosis and the post-mortem examination showed complete absence of the suprarenals. It is to be noted, however, that there was a horseshoe kidney situated opposite the sacral prominence. Martini states that he examined the kidney carefully for aberrant suprarenal tissue and was unable to find any trace of it. In spite of this statement a critical reading of the report leads one to believe that the aberrant suprarenal tissue, which must have been present, had been overlooked.

The aplasia or hypoplasia of the glands in conditions of anencephaly and similar defects of the central nervous system is well authenticated and is of much greater interest on account of the fact that a proper explanation of the changes in these conditions may ultimately lead us to a clearer view of the functions of the cortical portion of the glands.

Morgagni was the first to note the small size or absence of suprarenals in fetuses in which the cerebral hemispheres failed to develop. Since that time many authors have confirmed the observation, although the majority have found hypoplasia, rather than complete absence, of the organs. It is only within recent years that a true explanation of the character of the hypoplasia has been given. Zander in 1890 gave a careful review of the subject up to that date and gives an extensive study of the proportions of suprarenals to kidney in normal and abnormal fetuses at various periods of fetal life. In 1911 Elliott and Armour, in a paper which described for the first time the postnatal changes in the human suprarenals, described in detail the glands in a full term anencephalic fetus. They found that although small, about one-sixth the

normal size, the shape was exactly that of a child of one year. There was a full development of the medulla and an absence of fetal cortex. More recently Meyer, Kern, Veit and Landau(*a*) have investigated the condition carefully and have shown conclusively that the hypoplasia in these cases did not involve the whole gland but only the cortex, that on the other hand the medulla in these embryos was hyperplastic as compared with embryos of the same age. Landau's explanation seems the most plausible one. He points out that the physiological development of the human suprarenal may be divided into two stages; in the first stage there is a general increase in size, that is during the first half of intra-uterine life; in the second half of intra-uterine life and for some considerable time after birth the general increase in size gives place to an increase in surface which results in the characteristic folded shape of the fully developed gland. As Elliott and others have pointed out, the most important change after birth is the degeneration of the inner cortical layers (fetal reticulata and fasciculata) to make room for the rapidly developing medulla, the cortex regenerating from the glomerulosa to form the permanent cortex of the gland. Landau in his studies on anencephaly has shown that the pathological changes in the gland seem to date from about the sixth month of pregnancy. Meyer places the change at the fifth month. Thus, in these cases the development of the suprarenals pursues a normal course until about the mid-period of fetal life, when the whole process takes on a more rapid tempo which parallels the changes which occur in the normal infant after birth. The primary reticulata and fasciculata degenerates rapidly, the medulla undergoes hyperplasia and at full term the fetus with extreme anencephaly shows a miniature suprarenal with a medulla well developed, with complete disappearance of fetal fasciculata and reticulata and with a thin cortex consisting of glomerulosa and newly formed fasciculata corresponding in the proportion of the various parts to that of an infant many months after birth. In fact, the change which has been found may be regarded as a hurrying forward of the changes during the second half of fetal life which normally do not take place until after birth. The result is a gland which is only

Fig. 1. Photograph of a section of the right suprarenal of an anencephalous fetus of about the eighth month.

slightly larger than that of the fifth month but with a modeling like the normal gland with a fully developed medulla. Weigert describes it very well when he says, "Der Durchschnitt einer solchen Hemicephalennebenniere sieht ganz dem einer normalen ähnlich, nur dass alles gewissermaassen en miniature sich darstellt."

Fig. 1 is a section of the suprarenal of an anencephalus fetus of about the eighth month. It shows the typical folding of the fully developed gland. The medulla is beginning to show and the degeneration of the fetal reticulata and fasciculata is well advanced. The right gland measured 11 mm. x 13 mm. x 5 mm. in the formalin fixed specimen.

The degree of this change varies considerably in different cases of anencephaly or hemicephaly and it still remains to be shown what connection there is between this more rapid development of the gland and the cerebral defect. Zander's critical study of his large series with various cranial defects lead him to conclude that it was closely correlated with failure to develop of the anterior portion of the cerebral hemispheres.

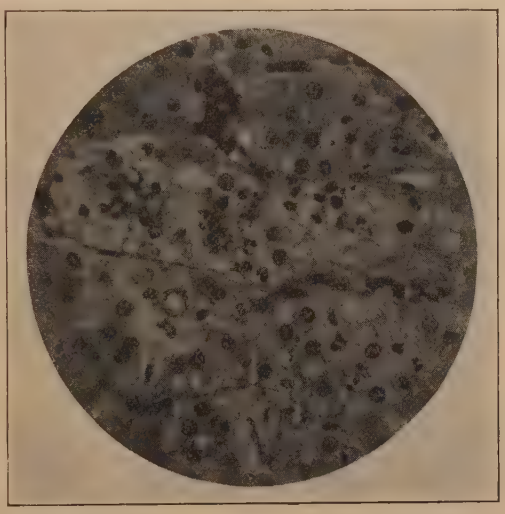

Fig. 2. Focal necroses in the zona fasciculata of a case of epidemic influenza.

Dystopias of the gland may involve the whole gland or simply the cortex. Rokitansky was the first to describe the presence of the suprarenals beneath the capsule of the kidneys. Schmorl has described a right suprarenal beneath the capsule of the liver. Other writers have found them embedded in kidney tissue. Accessory masses of suprarenal cortex are commonly found beneath the capsule of the kidney and between the renculi (Grawitz) although there is still some doubt as to whether all the tumors described as hypernephromata of the kidney are always suprarenal in origin. Besides occurring in the kidney they are also found in the broad ligament (Marchand) and the epididymis. Some aberrant masses may contain medulla but this is rare.

Pathological Chances in the Suprarenals as a Result of Infections and Intoxications.—Focal necroses are of common occurrence in the suprarenal cortex. They occur most frequently in the zona fasciculata and as Mallory has shown are similar to the focal necroses which occur in the spleen and other organs as a result of acute bacterial toxemias. Moschcowitz has described the condition also. Apparently regeneration may occur, as Mallory figures active mitoses occurring in the cortical

cells in the neighborhood of the necroses. Fig. 2 is a photograph from a typical area of focal necrosis in a case of influenzal bronchopneumonia of nine days' duration.

Edema of the suprarenals is of frequent occurrence in cases dying from acute infections. It is most prominent in the inner zone of the cortex and may be so marked as to increase the size and weight of the gland.

In all acute infective conditions one meets with marked congestion of the sinusoids. It is most pronounced in the zona reticulata but is not necessarily confined to that. A step further occurs in the presence of small focal hemorrhages which may occur anywhere in the cortex. Massive hemorrhage into the glands is not uncommon. It has frequently been noted in the new-born and may be a cause of death in these cases. The hemorrhage may lead to complete destruction of the medulla so that the two glands are converted into blood cysts. Sometimes the cortex ruptures and extensive hemorrhage occurs into the perirenal and retroperitoneal tissue. The actual cause of massive suprarenal hemorrhage in the new-born has not been demonstrated, but a very plausible explanation is that it has resulted from too great or too precocious degeneration of the inner fetal cortex. Elliott and others have pointed out that as this degeneration progresses there is always excessive congestion of the degenerating cortex. In older individuals a variety of causes may act; the hemorrhage here is often in the nature of a hemorrhagic infarction and is due to the thrombosis or embolism of the vessels of the gland. Fig. 3 shows a hemorrhagic infarction due to embolism. An interesting form of hemorrhagic infarction was first emphasized by Kolisko, occurring in fatal cases of burns. Weiskotten has also reported cases but doubts if the condition is a true hemorrhagic infarction. This hemorrhage into the suprarenals as a result of burns may very well be the immediate cause of death as the amount of destruction of gland tissue is sometimes very great. Fig. 4 is a high-power photograph of a portion of the zona

Fig. 3. Hemorrhagic infarction of the left suprarenal due to embolism. There was a mural thrombus in the left ventricle and emboli in the cerebral vessels, in the left suprarenal artery and in the left femoral artery.

glomerulosa from a case of burns. The patient was an old man who was badly burned about the legs; first, second, and third degree burns were present. He lived nine days after the accident. Both suprarenals were swollen and hemorrhagic. There was extensive recent thrombosis of the veins, and microscopically there was focal exhaustion of the cortical lipoid with extensive necrosis and hemorrhage into both cortex and medulla. The photograph shows hemorrhage into a portion of the glomerulosa with blood corpuscles within the columns of cells. Hemorrhage may also occur in the hemorrhagic diatheses and in leucemia. has also been described in general venous stasis due to cardiac disease.

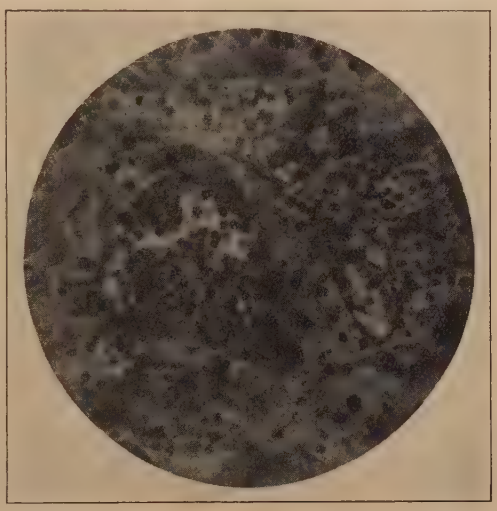

Fig. 4. Hemorrhage into the zona glomerulosa from a case of fatal burns.

Amyloid degeneration is as common in the suprarenals as in the spleen and liver. It is produced by the same causes, viz., chronic suppuration, tuberculosis and syphilis. As in the liver, the amyloid is deposited in the walls of the sinusoids. It is more marked in the fasciculata but may be found throughout the cortex and in the medulla; in the cortex the parenchymal cells are gradually compressed by the amyloid material.

Parenchymatous degeneration is common but often difficult to differentiate from postmortem change. In 1909 Oberndorfer described peculiar hyaline or colloid droplets in the medulla of suprarenals of twelve cases, ten of which were from acute infectious disease. He is in considerable doubt as to the interpretation of these droplets or granules and discusses whether they are of the nature of Russell's bodies, which they resemble closely, or are phagocyted red blood cells. These droplets vary in size from larger than the nucleus to quite small granules. We have seen them very commonly in influenza cases, but they are not confined to influenza as we have found them in pyemia, in bacillary dysentery and other acute bacterial infections. They have not been often noted, but if searched for in well fixed material they are not difficult to find. In hematoxylin-eosin staining they take a rose-red color, and like the Russell granulations, they are fuchsinophil. But they are best demonstrated by Mallory's phosphotungstic acid hematoxylin or Mallory's anilin blue connective tissue stain. With the former they are usually a deep blue: the latter stain brings out clearly that they are not homogeneous structures

as some stain blue, others red and others shades of orange. Sometimes blue and orange stain can be seen in the same droplet. They sometimes have a close resemblance to the hyaline droplets seen in renal epithelium in pathological conditions. Goldschmidt, from Oberndorfer's laboratory, published a more detailed account of these granules and definitely concluded that they are formed from phagocyted red cells, but from a study of the granules with the Mallory stains we think this very improbable. In the discussion of Oberndorfer's paper, Schmincke suggests that they are morphological evidence of secretory activity and they undoubtedly could suggest this explanation. Kawamura has described these droplets also. He found them very numerous in three cases of typhoid but met with them in other conditions although not constantly. However, they are not commonly present except in acute infectious conditions. We have noticed also that though usually in the medulla, they are not confined to it but may be found in the cortex. Fig. 5 is an oil immersion photograph of a group of granules from the medulla of a case of influenza of six days' duration. Fig. 6 is a similar photograph from the cortex of a case of general peritonitis.

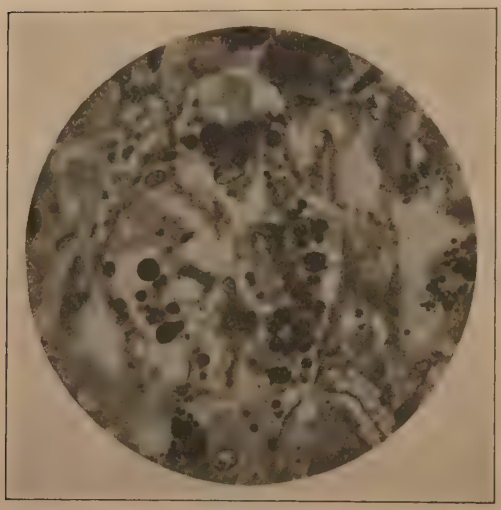

Fig. 5. Oil immersion photograph of the medulla of the suprarenal of a case of epidemic influenza stained by Mallory's phosphotungstic hematoxylin.

In recent years the attention of pathologists has been specially turned to the changes which occur in the constituents of the cortex and medulla of the gland in cases of patients that have died as the result of acute infections and intoxications and other pathological conditions. As a rule attention has been focused upon either cortex or medulla and no special attempt has been made to relate the one to the other. The most characteristic change in the cortex is the more or less complete disappearance of the cortical lipoid. Earlier writers, not understanding the significance of the lipoid of the cortex, failed to note the variations, and even Neusser in his monograph on the disease of the suprarenals, in Nothnagel's Encyclopedia, pays little attention to it. Beginning with 1910, however, more and more attention was paid to the question and there has now accumulated a considerable amount of literature upon the variation of the lipoid content of the cortical cells. This variation has been determined most commonly by applying to sections of the gland the ordinary fat stains, such as

Sudan, Scarlet R. or Nile blue sulphate, or by examining sections by polarized light for the determination of anisotropic lipoids. Such studies have been carried out by Loescheke, Goldzieher, Thomas, Weltman, Elliott(*g*), Kawamura and Landau(*b*). Others, notably Landau and McNee, have also determined chemically not only the total lipoid but the amount of cholesterol esters. From all these observations the general conclusion can be drawn that in acute septic conditions and acute infections or acute intoxications, the lipoid disappears more or less rapidly; that in more chronic infections it also disappears, but more slowly. In anemias and as a result

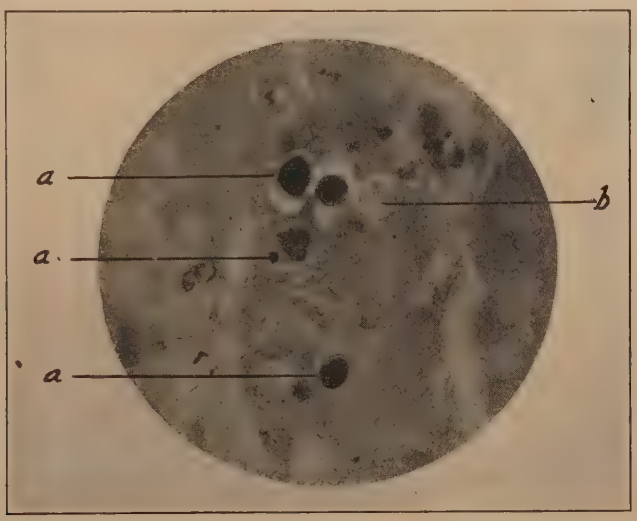

Fig. 6. Section of suprarenal cortex showing granules. Case of pulmonary abscess, abscess of liver, with general peritonitis. Stained with Mallory's phosphotungstic hematoxylin. *a*. Intracellular granules with centers stained; *b*. Granule unstained. Oil immersion photograph.

of severe hemorrhage it also diminishes or disappears. On the other hand, in all chronic circulatory conditions it is increased. This is true not only for chronic renal conditions with hypertrophied heart and arteriosclerosis but also for cardiac conditions with decompensation. The disappearance of the lipoid does not take place evenly throughout the cortex. As the exhaustion advances one finds focal areas still loaded with it whilst neighboring areas contain none. Finally only occasional cords of the fasciculata contain lipoid and at last the whole cortex gives no trace of lipoid material. We do not know really how these anisotropic fats of the cortex pass from the cells to the circulation but before there is complete exhaustion one sometimes sees in the neighborhood of the lipoid-holding cells small groups of endothelial leucocytes which seem loaded with fat, and this may be the method of transfer. Figs. 7 and 8 are low power

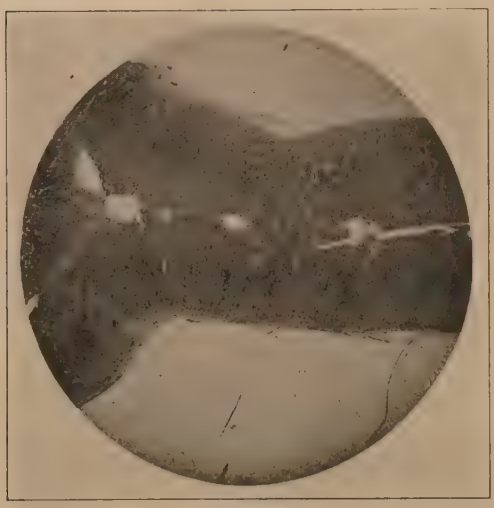

Fig. 7. Section of suprarenal from a case of influenza fourteen days' duration; double empyema, collapse of both lungs. Frozen section, stained scarlet and hematoxylin. The black areas in cortex are focal areas of lipoid.

photographs of suprarenals from influenza cases. The cells of the cortex containing lipoid appear black in the photograph.

Landau and McNee have determined quantitatively the amount of cholesterol and cholesterol esters in a large series of cases and their conclusions are that the total cholesterol content of the human suprarenal appears diminished in phthisis and other infectious diseases and in many neoplasms but that in inanition and pedatrophy it is high and in circulatory disturbances (contracted kidneys, arteriosclerotics, cardiopathics) it is very markedly increased. These variations are conditioned chiefly by variations in the cholesterol esters whilst the free cholesterol only slowly follows the changes in the cholesterol esters and is not affected by the momentary variations in them.

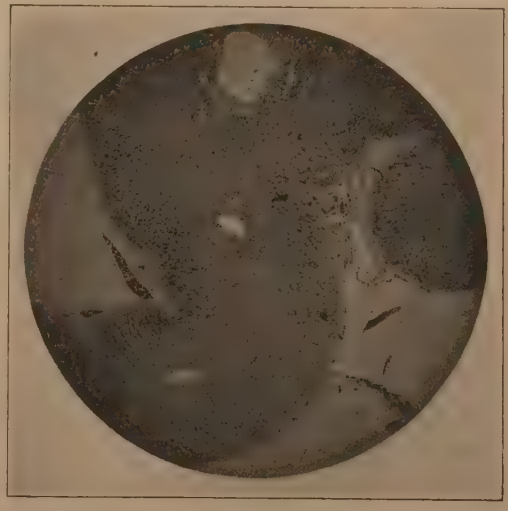

Fig. 8. Section of suprarenal from a case of influenzal bronchopneumonia of twenty-five days' duration; frozen section, stained scarlet red and hematoxylin. The black areas in cortex are focal areas of lipoid.

The degree of chromaphil staining of the suprarenal medulla, the amount of epinephrin and its variation in infectious diseases have also been subjects of careful study by a number of observers. Elliott's(*g*) quantitative observations were among the first. He gives the normal load of epinephrin at about 4.5 mg. per gland in the adult and he shows that the amount is lessened in many acute febrile conditions but could find no proof that it was increased above normal in any disease. Loeschke studied 100 cases for chrom reaction and epinephrin content and found a reduction or complete absence in all acute infections. Ingier and Schmorl found it diminished in acute

infections, slightly increased in arteriosclerosis and in various nephritides. Their variations, however, are slight and as they place the normal content lower than does Elliott(*g*) (2 mg. per gland) the relative content in the latter conditions appears higher. Pfeiffer in his experimental studies has shown also that the chromaphil tissues respond very quickly to toxic or nervous influences. He notes complete absence of the chrom reaction in seventy minutes to two and a half hours. On the other hand, he found complete regeneration of the reaction in forty-eight hours.

A necessary condition for the study of the chromaphil substance is fixation in solution containing chrom salts and immersion in the fixative not too many hours after death. Ciaccio(*a*) showed that the material disappeared fairly rapidly as a result of postmortem change. It is questionable therefore whether much reliance can be placed upon postmortem estimates of the epinephrin on account of this rapid disappearance. It is probably influenced by agonal conditions also.

Pfeiffer has made extensive experimental studies upon the variation of the lipoid and the chromaphil substances in rabbits, guinea pigs and rats as a result of different stimuli. In his experiments he used stimulation of the splanchnic, piqûre, the effect of removing both kidneys, the action of light after injection of photodynamic substances and finally, the effect of scalding. His conclusions have an interesting bearing upon the phenomena of disappearance of lipoid and chromaphil material in cortex and medulla. He regards these phenomena along with hyperemia as evidence of functional overactivity. Functional activity of the glands may be traced through all stages from the first induction of it to the end stage in which complete exhaustion of lipoid and chromaphil substance is attained. As a consequence of these observations Pfeiffer would hold that it is wrong to speak of death as due to acute suprarenal insufficiency. In all cases the insufficiency is secondary to changes in the body generally, and experimentally the condition is reversible, the lipoid and medullary secretion can be restored. Only where pathological conditions in the body lead to a persistent exhaustion of these substances can one speak of the influences of suprarenal insufficiency. These changes occur equally in cortex and medulla; the organ reacts as a whole but Pfeiffer's experiments show that the medullary function is the more labile, the cortical the more stable. Disappearance of chrom reaction may occur without evident diminution of lipoid, though where the stimulus is intense, the cortical reaction rapidly sets in. This is in direct contradiction of Landau's(*b*) view that the medullary reaction is always secondary to that of the cortex and is conditioned by cortical changes. Pfeiffer's experiments were carried out with the idea of proving that the suprarenal exhaustion was due to proteose intoxication. In his series, he used not only single animals, but animals parabiotically united, and in these parabiotic animals, where acute damage was applied to one animal, if

the union was complete, the suprarenals of the partner showed the same degree of change. He points out that it is a curious fact that the most varied forms of intoxication may lead to this characteristic morphological evidence of suprarenal exhaustion and that therefore it is much more plausible to regard this exhaustion as the result of some general systemic condition. He suggests that the disappearance of lipoid may be due to mobilization of these, brought about by the necessity of neutralizing excessive proteolytic enzymes in the blood, set free by the primary intoxication. This, however, is pure hypothesis and needs much more evidence for its foundation than we have at present.

The supposed connection between hypertrophy of the suprarenals and conditions of arteriosclerosis with hypertension, which was specially insisted on in the first instance by Schur and Wiesel(*c*) and by numerous French authors, has not been borne out by further study. The idea undoubtedly arose from the known effect of epinephrin upon the blood pressure. Study of the glands showed, however, no increase in the medulla but sometimes increase of cortex and especially the occurrence of adenomata of cortical material either outside the gland or within the medulla. Comparative studies have clearly shown that there is no relationship between adenomata of the cortex and hypertension although they may be somewhat commoner in older individuals.

Abscess formation due to metastatic foci in pyemic conditions is rare but is sometimes found.

Tuberculosis of the suprarenals is the characteristic finding in Addison's disease. Miliary tubercles are reported as not common, but careful study of the suprarenals in general miliary tuberculosis will usually reveal a few small foci. In Addison's disease, on the other hand, the process is a slow caseating one with apparent increase in size of the gland and areas of extensive fibrosis often with calcification.

Syphilitic disease of the suprarenals is not common, or at least has not been commonly reported. In acquired syphilis it usually consists in isolated or fused gummatous masses, with more or less destruction of the gland tissue. In congenital syphilis the suprarenals as a rule are literally swarming with the organisms. In spite of this, however, the histological change is relatively slight and not by any means as extensive as similar congenital lesions of the liver and lung. Focal necroses are fairly common, gummata also occur; sometimes areas of interstitial fibrosis are found. Simmonds(*b*) has described as the most common characteristic of congenital syphilis an infiltration and fibrosis of the capsule of the gland; what he designates perihypernephritis syphilitica.

Suprarenal Pathology in Addison's Disease.—Since the classical description of the pathology of the suprarenals in this disease by Addison(*b*) in 1855 an enormous amount of work upon the changes in the glands and the chromaphil system has been carried out. With all this work, however,

we can hardly say that we understand as yet the pathogenesis of morbus Addisonii nor the relative importance of the involvement of cortex or medulla in the production of the symptoms. A distinct step forward was taken when Star called attention to the presence of a persistent thymus in the adult in certain cases. Since Star's observation the attention of many authors has been directed to the coexistence of status thymolymphaticus and Addison's disease. Hedinger(*a*), for example, reports 15 cases in seven of which there was marked status thymolymphaticus, in five cases hyperplasia of the general lymphadenoid apparatus, and three cases in which the data in regard to thymus gland and lymph nodes were negative or uncertain. Kahn, Wiesel(*b*) and others have also reported cases where this association existed. The coexistence of the two morbid conditions has an important bearing upon the question of the relative importance of lesions of cortex and medulla in the causation of the disease, because in status thymolymphaticus there is a distinct hypoplasia of the general chromaphil system. A very puzzling fact in a typical case of Addison's disease is the extensive tuberculous destruction of both suprarenal glands with often comparatively slight tuberculosis of other organs. Elsässer(*a*) found isolated tuberculosis of the adrenals in 17 per cent of 549 cases in the literature. The only possible explanation of such an isolated tuberculosis is in a lowered resistance of the organ, due to insufficiency either congenital or acquired. Karakascheff reported cases in which cortical destruction was the chief condition and he argues in favor of the greater importance of the cortex in the pathogenesis of the disease. Wiesel(*b*), on the other hand, considers that destructive change in the cortex is necessary but that lesions of the chromaphil tissue must exist either within or without the gland. In a recent typical case with extensive caseation and fibrosis of the glands we were able to find isolated islands of apparently normal cortical material whilst no trace of medulla could be found. A great difficulty is to understand cases in which there is Addison's disease with reported normal suprarenals. Lewin in his monograph of 561 cases found 12 per cent without lesions of the suprarenals and since his analysis numerous other cases have been reported. The occurrence of destructive disease of the glands without Addison's disease can be explained on the view that the factor of safety in cortical material had not been overstepped and the general chromaphil system was normal or hyperplastic. The general asthenia and low blood pressure are commonly explained on the grounds of chromaphil insufficiency and the gastro-intestinal symptoms as secondary to the vasomotor disturbances consequent upon this insufficiency. The explanation of the pigmentation of the skin and mucous membranes present, on the other hand, considerable difficulty. It is true that the pigmentation varies in amount and may be absent. It is apt to be a manifestation of the later stages of the disease and so cannot rank in importance with the other symptoms, but it is such a

striking abnormality that it is extremely likely that a correct interpretation would throw a flood of light not only upon morbus Addisonii but also upon the whole question of suprarenal function. There is evidence that pigment production may be related to epinephrin. Melanin-like pigments can be produced by the action of oxydase ferments (tyrosinase) upon tyrosin and similar substances. Jaeger considered epinephrin to be the source of melanin pigments. Roger(*b*) recently has demonstrated a chromogen in horse suprarenals, which in the presence of oxygen gives a black material insoluble in alcohol and nondialyzable. He suggests that this black pigment is the cause of the pigmentation of Addison's disease and that in normal subjects the gland abstracts the pigment and converts it into its chromogen. This, however, is pure hypothesis and the difficulty of correlating Addison pigmentation with epinephrin or similar substances is that it is just in the cases in which we know there must be diminished epinephrin secretion that the pigment appears. That it is due to local cell metabolism, possibly of an oxidative character, upon substances in the general circulation is indicated by the effect of pressure and irritation upon the development of the pigmentation of the skin. The common cause of Addison's disease is of course tuberculosis, but numerous cases are reported in which the suprarenal destruction has been produced by other pathological conditions, such as syphilis, hemorrhage or new growths.

Tumors of the Suprarenals.—From the cortex tumors arise which more or less resemble normal cortical tissue depending upon the degree of anaplastic alteration which has developed. There is possibly an unbroken series between hyperplasia of the cortex through cortical adenomata (in well marked examples Virchow's(*b*) struma suprarenalis) to the true suprarenal hypernephromata which are definitely malignant.

Sarcomata, lymphosarcomata, alveolar sarcomata, endotheliomata of the cortex have been described. In many instances the description of these tumors leaves one in doubt as to whether they are to be regarded as true sarcomata or as hypernephromata with an excessive degree of anaplastic change. Woolley(*a*) in 1902 described a malignant tumor originating from the suprarenal cortex which locally showed the characters of a true hypernephroma but which in its distant metastases had the appearance of a true sarcoma. He and Adami(*b*) would designate such tumors as mesotheliomata and explain this extreme anaplasia as due to a reversion of the cells to the original mesoblastic type. The hypernephromata are well established. They usually show in the gross a strikingly variegated appearance; the general tone is yellow but areas of hemorrhagic change with various tints of brown and red are seen throughout it: microscopically the tumor is made up of cells with a foamy protoplasm due to the presence of lipoids and glycogen droplets. The cells more or less mimic the zona glomerulosa or zona fasciculata of the normal gland with irregular columns of cells resting upon sinusoidal blood vessels. There is a great

variation in size of the cells and the nuclei and giant nuclei, as well as true tumor giant cells are frequent.

Hypernephromata and conditions of cortical hyperplasia often have an interesting effect upon the sexual glands and secondary sexual character which will be referred to later.

The tumors of the suprarenal medulla, aside from hyperplastic change or tumor formation arising in the cortical tissue, carried into the developing organ by the vessels are all of a very special type, genetically related as the medulla is to the sympathetic system and the chromaphil tissue of the sympathetic trunk. The three types of cells present in the medulla may each give rise to tumors, viz., the embryonic cells of the sympathetic system sympathogonia, the ganglion cells of the sympathetic system and the chromaphil cells themselves. Herxheimer designates the three types of tumors according to the stage of development: neuroblastomata from the sympathogonia, ganglioneuromata in which more fully differentiated ganglion cells are present, and paragangliomata those which arise from and are formed of cells with chromaphil reaction. The first form, the unripe type, the second and third, the ripe type. The paragangliomata are rare tumors; not many have been described, but their rarity in the literature is probably due to the fact that they are small and often overlooked. They occur in adult life, are usually of accidental finding and are not malignant. They consist of cells more or less polyhedrous in form with indistinct cell boundaries, large well stained nuclei; some cases are described where true tumor giant cells occur. They are characterized by the presence of the chrom reaction and epinephrin has been demonstrated in them. They not only occur in the medulla of the suprarenal but may develop in other parts of the paraganglionic system. The chromaphil reaction varies very much in different parts of the tumor and often one finds collections of small cells, evidently sympathogonia, amongst the larger tumor cells; in several cases they have shown cystic degeneration. An interesting point is that in a number of cases of von Recklinghausen's neurofibromatosis, either paragangliomata or hyperplasia of the chromaphil tissue of the suprarenal medulla has been found. The tumors of the chromaphil tissue, however, are to be regarded rather as an indication of a general systemic involvement of the sympathetic system, and not as the underlying cause of the neurofibromatosis. In addition, probably the majority of paragangliomata are not associated with von Recklinghausen's disease.

The second ripe type of medullary tumor is the ganglioneuromata. Herxheimer in 1914 collected records of twenty-nine cases; only eleven of these were in the suprarenal medulla or closely associated with the glands. The type of cell is evidently the sympathetic ganglion cell but they also contain more or less numerous non-medullated nerve fibers. The ganglion cells are often distinctly embryonic in type, frequently much

larger than normal cells, and may contain numerous nuclei and are destitute of lipochrome pigment. The majority of them are non-malignant but occasional cases have shown local infiltrative growth and some are definitely malignant. As a rule they occur under twenty years of age, although they have been found in later life.

The third type of tumor of the suprarenal medulla is that which is described as neuroblastoma. These are distinctly of an unripe type and consist of small cells similar to the sympathogonia. They were first described as lymphosarcomata or small round-celled sarcomata and they are still apt to be mistaken for small round-celled sarcomata. The application of special stains and careful study of their histology revealed the fact that they were derived from the sympathogonia. The nuclei are similar in size to those of these cells. They have comparatively little protoplasm and show a special tendency to arrange in rosette-like nests. These rosettes are embedded in a fibrillar material which, with special stains, can be demonstrated to be neurofibrils. These tumors are all malignant and apparently all of congenital origin. Herxheimer in his review cites twenty-eight undoubted cases and adds a twenty-ninth. Wright, who described four cases, only two of which Herxheimer places on his list, considered that tumors of this class were probably much more common than supposed. In twenty-eight cases cited by Herxheimer the eldest was nine years; twelve of them had not reached the third month at the time of their death. Lambert lists twenty-seven cases and adds another. Undoubtedly many of these tumors have been overlooked or wrongly described. Ewing points out that probably most of the retroperitoneal round-celled sarcomata of infants belong in this class.

A rare primary malignant tumor of the suprarenal medulla is the melanoma. Quite a number of cases have been described; frequently both glands show the tumor. Luksch(*b*) has described small brownish, non-malignant cortical tumors containing melanin. The origin of these tumors is obscure. Tuczek made a special study of the pigment of these tumors and showed that it is certainly melanin, whilst the pigment of the zona reticulata is a lipochrome. He believes that such tumors, as well as the rare primary melanomata of the brain, may be derived from pigmented neuroepithelium; that is, that they originate ultimately from ectodermal elements. McLachlan is opposed to this view and considers that they must be derived from wandering chromatophore cells which have been included in the developing suprarenals.

Metastatic carcinomata and sarcomata are not uncommon in the suprarenals, but unless they are so extensive as to lead to extensive destruction of the glands with the development of morbus Addisonii, they are not of any special significance.

The Pathology of the Suprarenals in Its Relationship to Other Endocrin Glands.—A number of important observations have been made

from time to time which indicate that disease of one endocrin gland may involve other glands of the same type. Although the evidence is often very striking the exact interpretation is still obscure. Probably the interrelationship of the suprarenals and the sexual glands have been demonstrated most clearly. French investigators were the first to direct attention to the influence of overfunction of the cortical portion of the suprarenal upon the secondary sexual characters under the name syndrôme génito-surrénale. Bulloch and Sequeira(*a*) have collected a number of typical examples, and more recently Glynn has added others to Bulloch and Sequeira's list and has carefully analyzed all reported cases to the date of his publication. In children the result of these observations shows that in females there is developed not only sexual precocity, e.g., menstruation, development of external genital organs and breasts, but also the development of male characters, notably hirsutes upon the face, axillæ and pubes. In males there is also sexual precocity but male characters are emphasized, the child's muscular development becomes abnormal, showing the characters of an infant Hercules. In adult females, suprarenal hypernephromata lead to the alteration of the secondary sexual characters towards the male side. Menstruation ceases, the breasts atrophy, extensive growth of hair develops upon the face, the voice frequently changes, the muscular development may become marked and the temperament becomes aggressively male in character. On the other hand, there is very little evidence of the effect of suprarenal hypernephromata upon adult males. Finally, Glynn has shown that there is a close association between cortical hyperplasia and female pseudo-hermaphroditism.

An interesting relationship between suprarenal pathology and general growth is seen in the condition described by Gilford as progeria and by Variot and Pironneau as nanisme type senile. Three cases have been described, two by Gilford and one by the French authors. In each case growth ceased before the fifth year of life, the hair of the head, eyebrows, eyelashes and trunk was almost entirely absent, the skin was dry and wrinkled, the fat completely absent so that the muscles and tendons stood out prominently, the genital organs were hypoplastic and at the end there was extreme feebleness. In Gilford's case the autopsy showed fibrous atrophy of the suprarenals. The French case showed fibrous changes not only in the suprarenals but also in the spleen, lymph glands, pancreas, thyroid and hypophysis. Although the authors relate the curious condition to the suprarenal change, the observations are too few in number and the histological studies too superficial to enable one to speak with any positiveness in regard to their explanation. It is quite possible that this senile type of nanism is a manifestation of pluriglandular disease rather than simple involvement of the suprarenals.

The influence of thyroid disease upon suprarenals must be marked, but as yet no satisfactory morphological evidence of this has been secured.

In tumors of the pituitary, especially in acromegaly, occasional observations indicate that suprarenal change occurs. Delille states that hypertrophy of the suprarenals is often found in acromegalics. Fischer found in two cases enormous hypertrophy of the suprarenals, in one case this organ being five times as large as normal, and he believes that there was true excess of suprarenal tissue beyond what would be accounted for by the general splanchnomegaly. He quotes Stadelmann(*b*) as finding cystic suprarenals in an acromegalic but a reference to Stadelmann's article shows that the change was of the usual postmortem character.

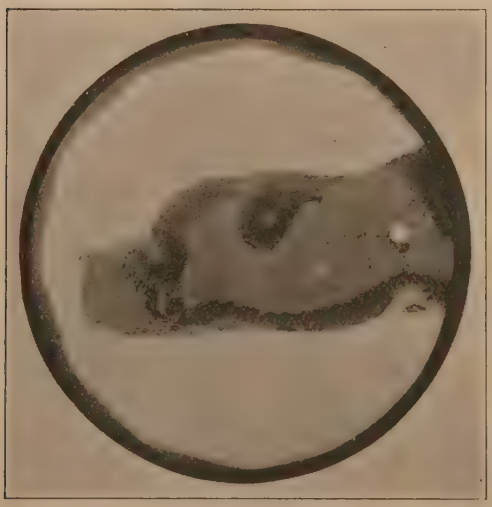

Fig. 9. Photograph of a portion of the left suprarenal from a case of cystic tumor of the hypophysis, stained with scarlet red and hematoxylin.

Fig. 9 is a photograph of an interesting suprarenal from a case which died suddenly in the wards of the Toronto General Hospital, and illustrates a possible relationship between pituitary and suprarenal. The patient was a man, aged 28, who entered the hospital with symptoms of brain tumor and died suddenly. The man presented no abnormality except that the pubic hair was sparse and transverse in arrangement. The hair on the face and axillæ was also sparse. He was married and the father of several children. His blood pressure was 110, S. and 85, D. The necropsy revealed a large cystic tumor of the hypophysis. The thymus was present and weighed 18 grammes but there was no evident hyperplasia of the lymphadenoid apparatus. The suprarenals were small and the section shows a strikingly narrow cortex heavily loaded with lipoid and a hypertrophied medulla. It would seem as if in this case the relative proportions of the cortex and medulla had been influenced either by the degenerative changes in the hypophysis or by the condition of partial status thymolymphaticus.

In status thymolymphaticus, as indicated in the discussion of Addison's disease, there is a special tendency for tuberculous infection to invade the suprarenal glands.

In diabetes no special morphological change in the suprarenals has been described.

Addison's Disease . . . . . *Benson A. Cohoe*

Introduction—Etiology—Pathology—Pathogenesis—Symptomatology—Course—Diagnosis—Prognosis—Treatment.

Clinical Syndromes due to Suprarenal Diseases

Addison's Disease

BENSON A. COHOE

PITTSBURGH

Introduction

A fundamental advance in the development of our knowledge of the clinical aspects of the diseases of the ductless glands was made when Thomas Addison(*b*), of Guy's Hospital, in 1855, published his classic treatise, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules." His observations upon an obscure clinical condition, characterized by profound asthenia, severe gastro-intestinal disturbances, and a peculiar bronzing of the skin, led to his discovery of the association of this syndrome with a diseased condition of the suprarenal glands. The concise definition of the clinical features of the disease, as portrayed by Addison, comprises all the essentials: "The disease develops in the third or fourth decade of life, usually quite insidiously, with adynamia and apathy. To these are added disturbances of the digestive tract (constipation, often alternating with diarrheas), and pigmenting of the skin and mucous membranes: the patients succumb under a gradually increasing cachexia, not rarely with stormy terminal manifestations; autopsy almost always shows disease of both suprarenals, mostly tuberculous caseation."

This important observation of Addison has had a far-reaching influence, not only upon clinical medicine, but upon the pre-clinical sciences as well. The interest of the clinicians was quickly aroused into recognizing clinical forms of the disease, and into theorizing upon the obscure underlying pathogenesis. Among the earlier physicians confirming the observations of Addison were Wilks, Greenhow, Hutchinson, and Isaac Taylor in America (1856). The caption "Addison's Disease" was first employed by Trousseau (1856). Clinicians since the time of Addison have contributed many facts concerning the clinical phenomena of the disease, which have been co-ordinated by the labors of Neusser, Lewin,

Bramwell, Rolleston and others. It is, however, to the pre-clinical scientists, especially to the physiologists and pathologists, that the advance in our knowledge of the disease, imperfect as it is in many respects, is in large measure owing. The physiologists, on their part, were stimulated into undertaking investigations directed towards the elucidation of the obscure function of the suprarenal glands, and the epoch-making research of Brown-Séquard in relation to the vital importance of these organs, played no small rôle in the subsequent formulation of the modern conception of the theory of internal secretion. The later experimental researches of Tizzoni, Abelous and Langlois, Oliver and Schäfer and Takamine, and more recently of Elliott, Gley, Stewart, Vincent, Cannon, Hoskins and numerous other investigators have produced many facts of prime importance to our interpretation of the clinical features of the disease, while the anatomical research of Kohn and of Wiesel has had an important bearing upon our conception of the pathogenesis. Although it has not proven possible, as yet, to correlate all of the accumulated facts arising from clinical, pathological, physiological and anatomical investigations, a very considerable progress has already been made in that direction. Meanwhile, after the lapse of almost three quarters of a century of painstaking and exhaustive research, from which have arisen many inadequate hypotheses concerning the origin of the malady, the significant fact remains as a remarkable tribute to the scientific acumen of Addison, that his clinical description of the disease embraces almost all that we regard as essential at the present day, and further that his discovery of the association of a decreased function of the suprarenal gland with muscular and circulatory weakness still stands as probably the most important fact known concerning the function of this organ.

Etiology.—The disease is rare. Personal observations of the disease by the individual clinician are limited to a few cases, and even in large medical clinics less than one case a year may be noted. Osler remarks that only seventeen cases came under his observation in the United States. It occurs at all ages, in all races, and all climates, but is believed to be more common in the white races, and in Europe. The older statistics would seem to indicate that males are more often affected than females, in the proportion of about six to four. In Greenhow's analysis of 183 cases, there were 119 males and 64 females, but the statistics of the Bureau of Census for the United States, on the other hand, show that of 320 persons dying of the disease during the year 1917, in this country, 174 were females and 146 males. Of this number only 5 cases occurred in the colored race. The average annual death rate per 100,000 of the population for the decade 1900-1910 was 0.45, and the cases were equally distributed between urban and rural districts. As Addison pointed out, it is a disease of middle life, of the third or fourth decade, the majority of cases occurring between the twentieth and the fortieth years. Although

it rarely occurs in the extremes of life, cases have been reported in infants and in octogenarians. Among the 320 cases above noted, the greatest number of deaths (75) occurred during the sixth decade. Two cases had passed the eightieth year. No social class is exempt from the disease, but a large proportion of the cases appear to come from the working classes.

Among the predisposing causes commonly noted by writers are included such factors as depressing conditions of life, prolonged worry, or emotional shock, intoxications, alcoholism, heredity, and infections, especially malaria, influenza, pneumonia and tuberculosis; and more recently congenital anomalies of the chromaphil system. Only in rare instances, however, is there any substantial evidence that such factors play an important etiologic rôle. A few cases have been reported in which, following some shock or depression, the disease has developed and run an acute course. The strain of war has recently been alleged to be a factor in the frequent incidence of this disease among soldiers, but Ramond and François, from a study of such cases, are of the opinion that the great majority of these are ultimately tubercular in origin. Trauma, due to strains or injuries of the back or abdomen, has been known to precede the onset of the disease. Traumatic hemorrhage into the gland substance and thrombosis of the adrenal vessels have been regarded, not infrequently, as predisposing causes. Heredity is probably not a significant factor, although a few isolated observations have been made of the occurrence of the disease in different members of the same family,—in one instance, in the mother and four children (Fleming and Miller). Within recent years, there has accumulated considerable evidence for regarding a congenital anomaly of the chromaphil system as an important predisposing factor.

In the great majority of cases (88 per cent), some destructive lesion of the suprarenal glands has been found at autopsy. Tuberculosis of the glands far exceeds other causes, atrophy ranking second. Syphilitic lesions (gummata), new growths, or other organic changes, either involving the suprarenals or the solar plexus and the semilunar ganglia, have been noted in other instances. At times, no pathological lesion of the glands has been encountered, an observation which has led some authorities to assume that a purely functional disturbance of the glands may, in certain cases, be the etiological factor.

Pathology.—Pathological studies have not served to establish the presence of any constant lesion of the suprarenal glands in this disease. Autopsy records have shown that tuberculosis is the most common finding, but normal glands have been occasionally reported (12 per cent in Lewin's series). Atrophy of the gland is frequently encountered. Other lesions are rare. Rolleston has summarized the various anatomical changes found in the suprarenal glands post mortem, in the order of frequency of oc-

currence as : (1) the fibro-caseous lesion, due to tuberculosis; (2) simple atrophy; (3) chronic interstitial inflammation leading to atrophy; (4) malignant disease, invading the capsules, including Addison's case of malignant nodule compressing the suprarenal vein; (5) blood extravasated into the suprarenal bodies; (6) no lesion of the suprarenal bodies themselves, but pressure, or inflammation, involving the semilunar ganglia.

In a study of 561 autopsy reports in Addison's disease, Lewin found tuberculosis of the glands present in 75 per cent of the cases. Some authorities believe the incidence to be even greater. The lesion is usually bilateral, although, at times, only one gland may be affected. In Addison's original series of eleven cases, five showed caseous tubercle of both suprarenals, while in one case, only one gland was diseased. There is reason to believe that the suprarenals may, in some cases, be primarily affected with the tuberculous process; Elsässer(*b*), in 549 cases, found isolated tuberculosis in 17 per cent of the cases. More frequently tuberculous foci are found in other parts of the body especially the lungs (43 per cent, Elsässer), peritoneum, bones and genito-urinary tract. It is thought that the suprarenals may become infected from the neighboring mesenteric glands in tuberculous subjects, or from the vertebrae, since some cases have been associated with caries of the spine. The tuberculous process affects both the cortex and medulla of the gland, in varying degree, with more or less complete caseation, or with softening, fibrosis, or calcification. Tubercle bacilli have been frequently found in these foci. Macroscopically, the glands may be greatly diminished in size, or in some instances enlarged, presenting the appearance of tumors. The gland parenchyma shows varying degrees of destruction, the medulla and cortex being uniformly involved, as a rule, but in some cases, chiefly cortex, or chiefly medulla have been found affected.

Atrophy of the gland is the second most frequent lesion found at autopsy. Bittorf(*a*) was able to collect 50 cases of simple atrophy. Macroscopically, in such cases, the gland is greatly diminished in size, at times being less than a millimeter in thickness. The normal shape may be preserved, or the gland may have become entirely shrunken and fused with the surrounding tissues. In some instances, it may have been reduced to a small mass of fat, or one suprarenal may have wholly disappeared. Bittorf states that in all cases the lesion is bilateral. There may be either (1) a simple atrophy, or (2) a chronic interstitial inflammatory type of atrophy of the gland parenchyma, resembling a cirrhosis. In the simple atrophy the alterations in the parenchyma may be only slight, of the nature of an aplasia, or of the absence of one or more layers of the parenchyma. In other cases fatty degeneration or necrosis may be found. Lymphocytic foci have been noted. In the inflammatory type, the parenchyma cells show various forms of degeneration, with a marked increase in the intercellular fibrous tissue.

Neoplasms of the suprarenal glands, both primary and secondary, rank next in frequency to tuberculosis and atrophy. Carcinoma, sarcoma, hypernephroma, perithelioma, and neuroblastoma have all been noted in cases of the disease. Syphilitic lesions, usually in the form of gummata, with caseation, fibrosis, and infiltration of the surrounding tissues, have been described in a few instances. Esser found gummata in the suprarenals of a new born infant, with symptoms resembling those of Addison's disease. Other rare pathological changes observed in the glands in this disease are echinococcus cyst, mycosis fungoides, and amyloid degeneration. Roth has recently reported a fatal case of the disease, following an attack of pneumonia. At autopsy abscesses were found in the suprarenals, from the pus of which the pneumococcus was grown. Thrombosis of the suprarenal veins has been noted by Straub(*b*) in an acute and fatal form of Addison's disease.

More recently, as a result of the fundamental observations of Kohn (*b*), Wiesel(*d*), and others, on the chromaphil tissue of the body, the attention of pathologists has been directed towards careful histochemical study of the entire chromaphil system in cases of Addison's disease. Wiesel first described extensive degenerative changes, and destruction of the chromaphil cells, occurring not only in the medulla of the suprarenal, but also in the chromaphil tissue of the sympathetic (thoracico-lumbar) system, in several cases of this disease. In one case with clinical symptoms of Addison's disease, in which, at autopsy, no lesion of the suprarenal glands was demonstrable, he found an entire absence of certain parts of the chromaphil tissue outside of the glands. According to Wiesel the chromaphil cells may entirely disappear from the sympathetic system, and the ganglion cells may yield a chromaphil reaction, a phenomenon regarded by Wiesel as compensatory, due to the loss of chromaphil tissue.

In a small proportion of cases extensive alterations are found in the sympathetic system. The semilunar ganglia and solar plexus may show degenerative changes, the result of invasion by tuberculous or inflammatory processes, or pressure by tumors, and may become embedded in cicatricial tissue (Edel). The lesions of the ganglia consist in changes in the ganglion cells, in the vessels, and in the connective tissue sheaths. Cellular infiltration, connective tissue proliferation, and thickening of the capsules of the ganglion cells and of the nerve sheaths; pigment atrophy and fatty degeneration of the ganglion cells, and degeneration of the nerve fibers have been described. Fleiner, in two cases of Addison's disease, was able to trace the degenerative process into the central nervous system, in the spinal ganglia, and the extramedullary portions of the posterior roots, in the vagus, and in a few peripheral spinal nerves. He found no important changes in the spinal cord. Other observers have described alterations in the spinal cord, but some authorities (v. Kahlden)

regard these as not a specific result of suprarenal disease, since such changes have been commonly noted in other conditions.

Microchemical studies of the suprarenal glands, in regard to determining the epinephrin content of the medulla, and the lipoid content of the cortex in Addison's disease, have so far been limited in number, although considerable work has been accomplished in estimating these bodies in other pathological conditions by several observers. Elliott(*e*) has shown that the normal suprarenal of an adult man weighs between 3 and 4 gm. and contains 4-5 mg. of epinephrin. Lucksch(*c*) states that the epinephrin content of the gland is less in Addison's disease than in any other pathological condition. Sydenstricker, Delatour and Whipple observed that tuberculous disease of one suprarenal may be associated with an increased epinephrin content of the intact gland.

The pathological changes in other organs in Addison's disease are not of great importance, and are such as usually occur in prolonged illness. The spleen may be enlarged. The heart frequently shows atrophic changes. Tuberculosis of the lungs, and of the mediastinal glands, is present in about half of the cases. Arteriosclerosis is regarded as an uncommon finding by most authorities, although Neusser states that atheromatous changes in the blood vessels are frequent, even in young persons, in this disease. The pigmentary changes in the skin and mucous membranes represent simply an augmentation of the normal pigment deposit. The pigment granules are found in the rete Malpighii, and are iron-free.

As yet, only a few observations have been recorded concerning the presence of pathological alterations in other endocrin glands in Addison's disease. A persistent thymus was first noted by Star, and has since been observed by several writers. It seems probable that *status thymicolymphaticus* is commonly associated with Addison's disease. A few observers have described cases of this kind. Alterations in the thyroid have been frequently noted, a decrease in size being found more often than an enlarged gland. The association of Addison's disease with hyperthyroidism has been observed in some instances. Dubois recently found lymphoid foci in the thyroid in six cases of Addison's disease. This formation of lymphatic tissue, with typical germinal centers, he regards as having some relation with *status lymphaticus*. Apart from atrophy of the gonads, which Falta(*c*) has stated to be almost invariably present, but few comments have been made in the literature concerning the involvement of the other endocrin glands in this disease.

Pathogenesis.—The obscure pathogenesis of this disease has proven an incentive for much speculation and theorizing upon the part of clinicians, and for extensive experimental research upon the part of investigators in the various pre-clinical fields. The history of the development of the modern theory of the disease forms an interesting chapter in medical science. Addison's original conception of the origin of the dis-

case was that any lesion of the suprarenal glands, sufficient in degree to interfere with their function, would give rise to the train of symptoms, in effect, a theory of *glandular inadequacy*. This view of Addison's was quickly subjected to much criticism by his contemporaries, Wilks and Greenhow, by reason of the fact that further pathological observations revealed examples of the disease, with clinical symptoms present, in which at autopsy no apparent disease of the suprarenal glands was demonstrable, and of other cases with advanced destructive lesions of the glands, in which the clinical symptoms of the disease had been wanting. Such conflicting observations led these authors to regard the genuine Morbus Addisonii as originating from a special lesion of the glands, and to maintain that no other lesion would give rise to the disease. According to their view, while the lesion in the suprarenal glands was special and primary, the clinical symptoms were produced by the secondary effects of the lesion on the neighboring sympathetic nerves, the semilunar ganglia, and the solar plexus. Addison, as well, somewhat altered his earlier theory, and was inclined to regard an involvement of the sympathetic system as a possible contributing factor in the causation of the disease. The finding of alterations in the sympathetic system gave rise to the so-called *nervous theory* of the origin of the disease, an hypothesis which found general favor in the early history of the disease. This theory appeared the more attractive by reason of the fact that the suprarenal glands, morphologically, were at that time commonly regarded as forming an essential part of the sympathetic system, the medulla being described as consisting almost exclusively of ganglion cells. Modifications of this theory were offered by Alezais and Arnaud and by Jaccoud. As pathological observations on the disease became extended, skepticism arose concerning the validity of this theory. It was found that in certain outspoken cases, no lesions in the sympathetic system could be discovered, and conversely that in some cases, which at autopsy showed irritation of the sympathetic ganglia, no clinical symptoms had been manifest.

Gradually the true glandular character of the suprarenal bodies was revealed, as a result of anatomical and physiological research, and with this knowledge the *glandular theory* of the disease became established. Brown-Séquard(*a*) in the year following Addison's communication, made the important observation that extirpation of both suprarenal glands in animals was invariably followed by death within one or two days, with symptoms of general weakness, convulsions, delirium and coma. He further noted that after the removal of both glands, life might be prolonged by the injection of the blood of healthy animals, and also that the death of an animal, from which one gland had been removed, could be hastened by the injection of the blood of animals, deprived of their glands. As a result of his investigations he concluded that the suprarenal glands are absolutely essential to life, and that the blood of animals, from which

the glands were excised, contained toxic substances. His views were strongly combated at the time but were later confirmed by the work of Tizzoni (1889) and other investigators. Somewhat similar researches by Abelous and Langlois (1892) have had an important bearing upon the interpretation of the glandular theory of the disease. These authors observed that the injection of the blood of frogs, dying as a result of extirpation of the suprarenals, into frogs recently deprived of these glands was markedly toxic, causing rapid paralysis and death, and further that a similar injection into healthy frogs with intact suprarenals produced only slight symptoms. These observations led them to believe that death was caused by the accumulation in the blood of toxic substances of an unknown nature, and to postulate the antitoxic function of the suprarenal glands, according to which the glands are concerned in the elaboration of a substance which is capable of neutralizing these toxic bodies present in the blood. Their experiments, further, afforded some evidence to show that the poisonous products of excessive muscular contraction are identical with the toxic substances accumulating in the body after the removal of the glands. In this connection it is of interest to note that Hoskins has more recently re-investigated these earlier observations of Abelous and Langlois, concerning the toxicity of the blood, and has found the blood of dogs dying of suprarenal deficiency to be in no degree toxic when injected into frogs.

The second method employed by the physiologists for investigating the function of the suprarenal glands, viz., the observation of the symptoms produced by the injection of the gland substance into animals, resulted in the epoch-making discovery by Oliver and Schäfer (1896) of the presence of a pressor substance in the medulla of the gland, from which they concluded that the suprarenals elaborate an internal secretion. In this manner physiological research, by the employment of two different experimental methods of investigating the function of the glands, viz., gland extirpation, and gland substance injection, has given rise to two possible interpretations of the glandular theory of the disease, (1) the *antitoxic theory* and (2) the *theory of internal secretion.* According to the antitoxic theory the symptoms of Addison's disease are due to the accumulation of poisonous products (e. g., of muscular activity), the removal or neutralization of which is the function of the suprarenal glands. A variant of this theory assumes that the suprarenal gland products represent these detoxicated substances. The antitoxic theory obtained wide recognition prior to the observations of Oliver and Schäfer and the subsequent postulation of the theory of internal secretion, according to which Addison's disease is due to an interference with, or a deficiency of, the normal secretion. This theory of the origin of the disease is now very generally accepted, while any detoxicating power which the gland may possibly possess is regarded as a function of the cortical tissue.

A comprehension of the dual nature of the suprarenal gland and of the occurrence of suprarenal tissue in various regions of the body, apart from the suprarenal gland proper, is indispensable to a clear understanding of the modern conception of the pathogenesis of the disease. The anatomists have shown that each human suprarenal is formed of two components, the cortex and the medulla, which differ from each other in morphological structure. In the lower vertebrates these components represent two separate and independent series of organs. The medulla of the gland is of neuroectodermal origin, derived from the anlage of the sympathetic system, and forms a part of the so-called chromaphil system, while the cortex is of mesodermic origin, and belongs to the interrenal system of organs. In mammals a mass of chromaphil cells (so called by virtue of their reaction to chromium salts) has become enclosed within the cortical tissue, forming the suprarenal gland. According to Kohn(*b*) the medullary substance is not properly a part of the suprarenal body, but simply a mass of chromaphil cells which have become insinuated into the suprarenal proper, or cortex. The suprarenal medulla represents only a portion of the chromaphil system of the body, and there is some reason to believe that there is more chromaphil tissue outside of the suprarenal glands than within them, since it is widely distributed in the body, occurring in the paraganglia of Kohn, the carotid gland, the plexus ganglia, and in the so-called accessory body of Zuckerkandl, and in minute masses along the sympathetic trunks. Stewart (1912), however, has cited evidence that the extra-suprarenal chromaphil tissue comprises but a small fraction of the total. The cortical tissue (interrenal system) is represented outside of the suprarenal proper by the so-called accessory "interrenal" bodies, which are also widely distributed, but less regular and constant in their occurrence than the chromaphil bodies. According to Schmorl accessory suprarenals are found in about 92 per cent of human cadavers. They are most commonly found at the hilus of the kidney, or within the kidney substance, along the suprarenal veins, and associated with the internal genitalia. True accessory suprarenals, formed of both cortical and medullary substance, are extremely rare. It is, moreover, believed that these two systems, the chromaphil (medulla) and interrenal (cortex) have entirely separate functions. Some observers regard the fusion of the two components in the higher vertebrates as having a physiological significance concerning the function of the gland as a whole, but no proof of this has been obtained. It has also been assumed, with respect to function, that what can be proven true of one part of the chromaphil or interrenal systems may be regarded as obtaining for the other portions of these systems. A pressor substance, similar to that found in the medulla, has been demonstrated in the extra-suprarenal chromaphil tissue by Biedl(*f*) and others.

It is, therefore, apparent that any consideration of the altered function of the suprarenal gland, as a basis for the interpretation of the phenomena

of the disease, must necessarily resolve itself into the broader viewpoint of the functions of the chromaphil system (medulla) and of the interrenal system (cortical tissue). Among the better known hypotheses concerning the function of the medulla are the following: (1) The *tonus theory,* which postulates that the internal secretion of the medulla (epinephrin) serves to maintain the normal blood pressure and to establish a state of tonus in smooth muscle fibers, innervated by the sympathetic nervous system in general. Considerable evidence has accumulated, however, to render this theory no longer tenable. The researches of Moore and Purinton(*b*) and others have shown that very small doses of epinephrin have a hypotensive action, and the more recent investigations seem to indicate that the circulating blood contains little or no epinephrin. Trendelenburg(*a*) found the epinephrin content of the blood from the carotid artery of the rabbit to be not more than one part in one or two billions, a quantity quite inactive in maintaining blood pressure. Moreover, the investigations of Hoskins(*a*), Gley(*f*) and others have offered evidence for the belief that epinephrin is not present in the blood in quantities sufficient to exert any appreciable effect on the sympathetic nervous system. The existence of a true epinephrinemia is doubted by many physiologists. The researches of Cannon(*a*) and his associates led them to believe, however, that during times of stress (e. g., the emotions of fear, pain, rage, etc.) the suprarenal is stimulated to secrete epinephrin in sufficient amounts to produce an action on the sympathetic system. This observation gave origin to (2) the *emergency theory,* according to which the function of the suprarenal medulla is the discharge of epinephrin in times of emergency only. There is considerable evidence of an experimental nature to substantiate this theory, although some investigators (Stewart(*c*), Gley) have failed to confirm various of Cannon's observations. A further possibility which has been suggested concerning the function of the medulla is that minute quantities of epinephrin are necessary for the metabolism of the tissues (Elliott(*e*))—(3) the *metabolic theory.* Sajous(*a*), since 1903, has maintained the view that epinephrin plays an important rôle in the respiratory mechanism, as a constituent of the hemoglobin, and has brought forward considerable evidence in support of this theory. The general conclusion which may be drawn from the results of an extensive experimental research concerning the function of the medulla, is that no satisfactory evidence has been adduced to show that the secretion of the chromaphil tissue (medulla) is of any service whatever in the normal state of the organism (Hoskins). The investigations of Stewart(*e*) appear to demonstrate that the secretion of epinephrin is not indispensable for life. This author, however, concludes that the effects, which epinephrin produces, are not gross effects, which are easily discernible, and that it is not possible in the present state of our knowledge to assign to any of these effects a rôle of definite physiological significance. The results of physiological re-

search at the present time, it would seem, do not appear to justify clinicians in ascribing the clinical symptoms of Addison's disease, in any general sense, to a diminished epinephrin secretion.

Concerning the function of the cortex (interrenal system) there is still less exact information. Three important hypotheses have been formulated, viz., that the function of the cortex is concerned with (1) the growth and development of the reproductive organs; (2) the neutralization of toxic substances; (3) the internal secretion of the medulla. The view is rather generally held that it is the cortex, and not the medulla, which is essential to life. It is known to be especially rich in lipoids and cholesterin esters, and Elliott has shown that these lipoids are stored and lost under conditions entirely different from those which govern the other fats in the body. There is some reason for suggesting (Vincent(*g*)) that these lipoid granules may yield a hormone possibly of the nature of a complex lecithalbumin, which influences the growth and nutrition of certain tissues, especially the organs of reproduction. A pressor substance, not epinephrin, but a cholesterin-like body, has been isolated from the cortical tissue by Voegtlin and Macht. It has also been assumed that the cortex possesses a detoxicating action, to the absence of which many writers have attributed the toxic symptoms frequently noted in the terminal stages of Addison's disease. No experimental evidence has been found, however, in proof of this detoxicating function of the cortical tissue.

The composite morphological structure of the suprarenal gland, and the presumably separate functions of the two constituents of the gland substance, have given rise to much speculation as to whether the Addisonian syndrome is caused by a destructive lesion primarily of the medullary, or of the cortical tissue, or whether an involvement of both tissues is necessary for the production of the symptom-complex. A final conclusion in regard to this question has not been reached, but the work of Wiesel(*d*) in this connection has proven most significant, and has served to establish the present trend of opinion. This author, in a careful histochemical study of six cases of Addison's disease, observed destruction of the chromaphil tissue in the medulla of the suprarenal and in the sympathetic system. No alterations, or at the most only slight, were found in the cortical tissue. In one case of clinical Addison's disease, in which no lesion of the suprarenal gland was detected at autopsy, he found a complete absence of certain other parts of the chromaphil system (the paraganglionic nodules), and in yet another case of tuberculosis of both suprarenals, in which the Addisonian syndrome had been absent clinically, he was able to demonstrate hypertrophy of the chromaphil tissue in the sympathetic system. In his opinion, the destructive lesion begins primarily in the chromaphil tissue, involving the cortex only secondarily. Nor is it necessary, he maintains, that the suprarenal chromaphil tissue (medulla) be diseased, since a lesion in the chromaphil tissue outside of the suprarenal

may suffice to give rise to the disease. Wiesel does not, however, deny the important rôle the cortex may play in the causation of the disease, and is of the opinion that for the production of some of the more severe clinical symptoms an involvement of the cortical tissue is necessary. At the present time this theory of *chromaphil cell inadequacy,* as the primary factor in the causation of the disease, is becoming quite generally accepted. If the theory be correct some of the cases of Addison's disease, without destructive lesions of the suprarenal glands, which were formerly regarded as of purely functional origin, might be explained on the basis of chromaphil inadequacy, since lesions in the chromaphil tissue outside of the suprarenal were probably overlooked by the earlier pathologists. Beitzke has brought forward confirmatory evidence in favor of this theory in a case of cancer of the suprarenals, without the Addisonian syndrome, in which the chromaphil tissues outside of the suprarenals were found intact. Some writers, while subscribing to the theory of chromaphil inadequacy, have extended it to embrace a lesion or irritation of the sympathetic nervous system, innervating the chromaphil tissue, suggesting that a lesion of these nervous structures may occasion a cessation of the gland function (Neusser).

In the opinion of some authorities a lesion of the cortex (interrenal system) is the factor of primary importance in the causation of the disease. Karakascheff has reported cases of Addison's disease, in which the destructive lesion mainly involved the cortical tissue. The clinical symptoms in these cases, in his opinion, were due to a loss of cortical cells, and he was unable to confirm Wiesel's findings of a general involvement of the chromaphil tissue. Löwy has also described a case of Addison's disease, running a very acute course, in which he attributed the clinical symptoms to destruction of cortical tissue, since he found only medullary tissue persisting in the suprarenals at autopsy. Scott believes that the destruction of the suprarenal medulla should not be especially harmful, in the presence of the wide occurrence of chromaphil tissue outside of the medulla. He accordingly ascribes the disease as due to a loss of cortical tissue, in view of the fact that accessory cortical tissue is a variable quantity. Bittorf(*a*), on the other hand, is inclined to regard the suprarenal as a single organ, no special part of which is of primary importance in the causation of the disease.

The recent observations of the frequency of the association of hypoplasia of the chromaphil system with *status thymicolymphaticus* have an especial interest in relation to the theory of chromaphil inadequacy as the cause of Addison's disease. Reports in the literature of the finding of an enlarged thymus, and of the occurrence of lymphocytic nodules in the thyroid gland (Dubois) appear to be on the increase. It has been suggested that the normal involution of the thymus is caused by a depressive influence of epinephrin upon this organ. If this hypothesis be true,

the theory of chromaphil inadequacy as the cause of Addison's disease would serve to explain the frequent occurrence of *status thymicolymphaticus* in patients with the disease, since such individuals have probably had from youth a condition of hypoplasia of the chromaphil tissue, rendering this tissue more vulnerable to the acquisition of secondary lesions of tuberculosis, etc., which in turn produce sufficient destruction of the suprarenal chromaphil tissue to give rise to the clinical symptoms of the disease. Wiesel(*d*) has observed that subjects with *status thymicolymphaticus* are especially prone to develop the disease.

Our inadequate knowledge of the functions of the medulla and of the cortex, or of any possible function of the gland as a whole, renders any satisfactory explanation of the single symptoms of the disease impossible at the present time. Some attempts at an explanation of these have, however, been made. Wiesel(*d*) has divided the symptoms into two groups: (1) those due to inadequacy of the chromaphil tissue (asthenia, low blood pressure, stenocardia, mental depression, hypoglycemia, and hypo-epinephrinemia); (2) those dependent upon a disturbance of the cortical tissue (gastro-intestinal symptoms, severe nervous symptoms, cachexia, exitus). The explanation of the pigmentation has proven especially difficult, the more so in view of the fact that the normal process of pigmentation is yet unknown. Wiesel has suggested that it may arise from a disturbance of the sympathetic innervation produced by an autointoxication arising from inadequacy of the suprarenal cortex. The pigment is generally regarded as belonging to the class of degenerative pigments—the melanins. Adami(*a*) has offered an hypothesis which attributes the pigmentation as due to chromaphil tissue inadequacy, assuming that in epinephrin deficiency the tyrosin and other aromatic products of protein decomposition, from which epinephrin may normally be manufactured, remain in the tissues and become transformed into melanin by the action of oxidases. Bittorf(*b*), similarly, believes that the increase in pigment formation is due to the presence in the epithelial cells of an oxidase (tyrosinase) which acts upon the aromatic bodies to form a melanin. The pigmentation has probably never been produced experimentally (Vincent(*f*)).

The asthenia has commonly been explained on the basis of chromaphil tissue inadequacy (Wiesel and others). Some writers (Paton(*c*)), however, attribute it to a loss of cortical function, basing such a view on the results of Biedl's experiments on the skate. The muscular weakness has been frequently produced experimentally by extirpation of the glands. Gruber(*d*) believes, as a result, of animal experimentation, that epinephrin exerts some specific action upon fatigued muscle other than that due to mere circulatory changes (vasodilatation of cardiac and skeletal muscles), possibly in the nature of neutralization or destruction of fatigue products. Cannon and Nice observed that epinephrin, injected in small

doses, or secreted by the glands during splanchnic stimulation, greatly improved the activity of fatigued muscles. On the whole, it would appear that the results of physiological research offer greater justification for attributing the asthenia to an epinephrin deficiency than is the case with the other symptoms of the disease. The adherents of the antitoxic theory of the disease explain the myasthenia as resulting from the toxic effects of muscular poisons, which the suprarenal in its normal state destroys.

The gastro-intestinal symptoms are generally regarded as arising from a disturbance of the cortical function. Another suggestion has been offered, that they are due to the irritation or paralysis of the abdominal sympathetic nervous system, especially of the *nervus splanchnicus*.

The arterial hypotension has been very generally ascribed to the epinephrin deficiency of the circulating blood (hypoepinephrinemia). Recent physiological investigations have, however, tended to show that the circulating blood does not contain sufficient epinephrin to exercise any influence of a hypertensive nature, and, indeed, to cast doubt upon the existence of a true epinephrinemia. Moreover, it has been demonstrated that epinephrin in small doses produces a fall in blood pressure. It appears evident that this widely accepted explanation of the hypotension is, in the light of experimental research, no longer tenable.

The nervous disturbances of the milder form have been regarded as due to chromaphil deficiency, while the more severe nervous manifestations have been attributed to a disturbed cortical function. The neuralgic pains (perirenal, epigastric) have been thought to be caused by pressure or irritation of the sympathetic nervous structures.

The hypothermia has been explained on the basis of low blood pressure. Another possible explanation has recently been offered by Cramer(*c*) who has attempted to show that the so-called thyroid-suprarenal apparatus is a factor in regulating the body temperature. In the absence of epinephrin discharge, a decreased glycogenolysis takes place. The validity of this hypothesis has not been confirmed.

In conclusion it may be emphasized that such interpretations of the symptoms of the disease are as yet purely theoretical, and must remain so until we acquire a more precise knowledge of the physiology of the suprarenal glands. Vincent(*g*), from the viewpoint of the physiologist, has recently voiced the opinion that the symptoms of Addison's disease can in no way be explained by the accumulated results of investigations in comparative anatomy and experimental physiology of the suprarenal glands.

Symptomatology.—In the typical case of the disease, the onset is extremely insidious, and the course essentially chronic. The clinical picture of the outspoken Addisonian syndrome, with its triad of cardinal symptoms—asthenia, gastro-intestinal disturbances, and melanoderma—develops slowly. The patient, who may or may not have been weakly from youth, begins to tire readily on slight exertion, and evinces a grow-

ing disinclination for physical or mental effort. His friends may notice that his complexion is becoming darker. Sooner or later, gastric disorders, with loss of appetite, nausea, epigastric discomfort, constipation or diarrhea, occur with increasing frequency, and may lead him to consult a physician. Gradually these initial symptoms, mild at first, and without uniformity in the order of their appearance or progress, in different individuals, become sufficiently marked in degree to enable the clinician to correlate them with the clinical entity of Addison's disease.

Addison's admirable portrayal of the initial stages of the disease merits quotation in this connection: "The patient, in most of the cases I have seen, has been observed gradually to fall off in general health; he becomes languid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large, but excessively soft and compressible; the body wastes, without, however, presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach, and there is occasional actual vomiting, which in one instance was both urgent and distressing; and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation. We may, indeed, suspect some malignant or strumous disease—we may be led to inquire into the condition of the so-called blood-making organs—but we discover no proof of organic changes anywhere; no enlargement of the spleen, thyroid, thymus or lymphatic glands; no evidence of renal disease, of purpura, or previous exhausting diarrhea, or ague, or any long-continued exposure to miasmatic influences; but with a more or less manifestation of the symptoms already enumerated, we discover a most remarkable and, so far as I know, characteristic discoloration taking place in the skin—sufficiently marked, indeed, as generally to have attracted the attention of the patient himself, or of the patient's friends."

The appearance of the cardinal symptoms may be accompanied, or preceded by, certain nervous and mental manifestations. The patient, as a rule, becomes markedly apathetic and listless, and may exhibit mental depression or increased irritability. The mental processes are retarded and the memory shows signs of impairment. Occasionally neuralgic pains in the lumbar region, or in the epigastrium, or extremities, occur; or, at times, headaches, fainting spells, tinnitus, vertigo and a more or less stubborn insomnia. There is no fixed order in the sequence of symptoms. As a rule, however, the asthenia precedes the melanoderma but not invariably. Occasionally the discoloration of the skin may be present for months before the appearance of the other symptoms. In other instances, the asthenia, gastro-intestinal disturbances and melanoderma develop together. In the majority of cases, the symptoms progress slowly

with a gradual increase in severity. Frequently, however, the mode of progress is paroxysmal, with remissions and intermissions in the severity of the symptoms.

The adynamia, or asthenia, is very generally regarded as the most characteristic and constant symptom of the disease. In almost all cases it occurs as the earliest indication of the onset. It is a psychic as well as a physical asthenia. In the early stage the patient complains of extreme lassitude, and of abnormal fatigue following physical or mental exertion. He may experience a constant fatigue, and become disinclined, or unable, to carry on his ordinary occupation. Langlois has laid stress upon the fact that while the patient, with this disease, may be able to make a short series of movements with considerable energy, he becomes almost instantly fatigued, in contrast to the patient with chronic pulmonary tuberculosis, who is able to carry on a sustained effort for a much longer period. When the disease becomes well established, the asthenia, as a rule, steadily progresses in degree of severity. In the earlier stages, however, it may occur over periods of varying length with intervals of remission, in which the patient may be able to resume his usual vocation. Fainting spells frequently occur, and are regarded as an expression of the asthenia. The muscular development and general nutrition of the patient frequently exhibit a marked contrast to the extreme degree of muscular prostration. In the later stages, the asthenia becomes extreme and forms an essential feature of the disease. The patient, sooner or later, becomes confined to his bed, and may be unable to rise, or in some instances, to feed himself, or to speak, or perform movements of any kind. A marked grade of asthenia may precede the appearance of the pigmentation by many months, rendering a diagnosis difficult. In exceptional cases muscular weakness may not be a prominent symptom. Tieken has recently observed a case with all the characteristic signs of Addison's disease, except asthenia, in which the muscular development and power were noted as fairly normal until within a few days before death.

The pigmentation of the skin is an important and striking sign of the disease, the presence of which some authorities have come to regard as a *sine qua non* of the Addisonian syndrome. It is believed to be rarely absent during some stage of the disease. Lewin, however, found it present in only 72 per cent of his series, a proportion which is generally regarded as lower than the true incidence (Bittorf(*a*)). In the chronic forms of the disease it is almost invariably found present in varying degree, but in the acute cases it is commonly absent. The discoloration of the skin begins inconspicuously, usually following the initial asthenia, and the gastro-intestinal symptoms. Not uncommonly, however, the pigmentation constitutes the earliest sign of the disease, and may first attract the attention of the patient or of his friends. At times it may be present

for months before the asthenia becomes noticeable. The melanoderma represents an exaggeration of the normal pigmentation of the skin, and while pervading more or less completely the entire integument of the body, occurs most markedly in those regions of the body which are normally pigmented, or in parts exposed to light or pressure. It is usually first evident on the face, neck, backs of the hands and fingers, especially on the knuckles. The areolæ of the nipples, the axillary folds, the extensor surfaces of joints, the genitalia, and the groins, may show a marked intensification of the normal pigmentation. Areas of the skin exposed to pressure or friction, as the waist line, the regions over the spinous processes and the ischial tuberosities, or parts of the skin pressed upon by the collar button, suspenders, belt or garters, become darkened. An area of scar tissue may become pigmented, or be surrounded by a dark areola. The *linea alba,* in pregnant women, frequently becomes a black line. The hair does not usually show pigmentary changes but cases have been reported in which it became darker. The skin of the scalp and other regions covered by hair, commonly escape pigmentation. The nail beds, palms, and soles are usually free, but pigmentation of the palms, with intensification along the folds, has been observed. The flexor surface of the phalangeal joints, in rare cases, shows pigmentation.

The nature of the discoloration of the skin has been variously described. Addison pictured it as a "dingy or smoky appearance, or various tints, or shades of deep amber or chestnut brown." It has commonly been described, in the earlier stages of the disease, as a dingy yellow tint. Straub(*b*) observed a general redness of the skin preceding the appearance of the pigmentation. As the disease progresses, the tint deepens from a light brown, or bronze, to a darker brown, in some cases assuming the dark hue of the negro. At times, a bluish or greenish tint has been noted. Although diffuse as a general rule, the melanoderma is rarely distributed uniformly over the trunk, but assumes a mottled or patchy character, frequently showing small areas of intense pigmentation resembling moles. Areas of leucoderma are frequently interspersed between the pigmented areas.

Pigmentation of the mucous membranes is almost constantly present, and is regarded as an especially important sign of the disease. It is usually distributed in the form of small spots or streaks, of a bluish black color. It occurs on the lips at the margin of the skin, sometimes spreading out from the angle of the mouth in a distinct streak; on the border of the tongue, the buccal mucosa, the gums, and soft palate; on the eyelids, and, rarely, the conjunctiva. The vaginal and rectal mucosa are occasionally pigmented. A patchy pigmentation of the serous membranes, occurring in the form of small black spots beneath the peritoneum of the mesentery and omentum, as well as pigmentation of the pia mater, has been noted in some instances.

As a rule the pigmentation deepens with the progress of the disease, but not uncommonly remissions in its intensity have been observed. A decrease in the melanoderma, following suprarenal gland therapy, has been recorded by numerous observers. In a few instances, it has been reported as having entirely disappeared under such treatment.

The gastro-intestinal disturbances constitute a prominent feature of the syndrome, but are, perhaps, the least constant of the triad of cardinal symptoms. They are variable both in occurrence and in intensity, throughout the course of the disease, and in occasional cases are entirely wanting. At times the disease may be ushered in with some digestive disturbance, either loss of appetite, or abnormal hunger, epigastric discomfort, nausea, eructations, and vomiting. As a rule, however, the asthenia has become well established by the time the gastric disorders make their appearance. The anorexia may be pronounced or in other rare instances the appetite may be voracious and accompanied by polydipsia and polyuria. The vomiting may occur with or without the taking of food, sometimes spontaneous in character, and in the later stages frequently uncontrollable, with the presence of blood, mucus or bile in the vomitus. The gastric symptoms are irregular in their occurrence and in the earlier stages show frequent remissions and exacerbations. Constipation is more common than diarrhea early in the disease, but the two conditions may alternate. Late in the disease, a profuse diarrhea is a common feature, at times occurring in crises and simulating a cholera nostras. The stools may contain excessive mucus, but rarely blood. Tenesmus has been occasionally noted although, in general, the diarrhea is not especially painful. Meteorism is frequently associated with the gastro-intestinal disturbances.

Abdominal tenderness and pain are common symptoms. The pain may be diffuse, or localized in the epigastrium, or loins, or elsewhere in the abdomen. Occasionally the pains are paroxysmal, suggesting gastric crises, or lead colic, and at other times gastric ulcer, or cholelithiasis, according to the localization. In a few cases, rigidity of the abdominal wall, associated with these pains, has produced the clinical picture of an acute peritonitis, a condition which has been observed to be followed within a few days by an *exitus lethalis.*

The symptoms referable to the nervous system may be slight at first, but almost invariably a psychic adynamia develops concurrently with the myasthenia. A striking apathy, and a loss of interest in the ordinary pursuits of life, and undue mental fatigue, are early features of the syndrome. Such patients are often classed as neurasthenics. An obstinate insomnia may prove troublesome, although in rare cases somnolence has been observed. Almost always the memory becomes defective. Mental depression, or mental excitation, and increased irritability and ill-humor, are common manifestations of the altered psyche. The mental deterioration,

or evidence of a psychomotor retardation, may be one of the first signs to arouse the suspicion of the patient's friends. In a case observed by the writer, the wife of the patient had noticed for a year previous to the admission of her husband to the hospital, that he had grown increasingly more irritable and quarrelsome, that his memory was greatly impaired, and his handwriting not so good as formerly, that he thought more slowly, and that his speech, although distinct, was slower. The special senses, especially smell, taste, and hearing, may occasionally show impairment. Paresthesias have at times been noted. There appears to be no characteristic alteration in the deep reflexes, although in a few instances they have been found to be sluggish.

As the disease progresses the cerebral manifestations become more pronounced. The mental deterioration may even attain a grade of imbecility, or, in isolated cases, a true dementia. Delirium is common towards the end, and choreiform or epileptiform convulsions sometimes occur. In a case reported by Langmead, which ran a rapidly fatal course, convulsions and rigidity, and all the symptoms of a meningitis, were observed. In general, marked psychical disturbances are more common in the acute than in the chronic forms of the disease. In the terminal stages, a violent delirium or maniacal excitement frequently precedes the onset of stupor, coma, and death, the "stormy terminal manifestations," to which Addison drew attention.

Neuralgic pains in various parts of the body are common in the disease. Pain in the lumbar region (*perirenal*) may be an early and important symptom. These may also occur in the abdomen (*epigastrium, hypochondrium*) or in the extremities. Occasionally arthralgias, with swelling of the joints, may lead to a diagnosis of arthritis (Ebstein).

The cardiac muscle shares in the general myasthenia, and the heart beat is usually found to be feeble and slightly accelerated. The heart sounds are faint, and in some advanced cases almost inaudible. The patients are subject to frequent paroxysmal attacks of dyspnea, without apparent cause. The slightest exertion may give rise to marked palpitation and dyspnea, often accompanied by stenocardia, as observed by Leva. Anemic murmurs, heard over the heart and blood vessels, have been noted, but are uncommon. There may be forcible pulsation over the abdominal aorta, forming a marked contrast to the feeble radial pulse. Towards the end, more or less cyanosis may be present, with increasing weakness of the cardiac muscle. The patient may die in a syncopal attack. The pulse, as Addison stated, is "small, feeble, or perhaps somewhat large, but exceedingly soft and compressible." In the late stages, the radial pulse may be imperceptible. Arteriosclerosis has not been commonly observed in Addison's disease in any marked degree.

Arterial hypotension is regarded as an important sign of the disease, but reports of the finding of fairly normal blood-pressure readings

in this condition seem to be increasing in frequency in the literature. The hypotension had been commented upon by clinicians for many years before the first sphygmomanometer readings were made by Turner (1899). In a small series of blood-pressure readings, collected from hospital records by the writer, the average systolic pressure was found to be 105^{mm}, and the diastolic 75^{mm}. Janeway has reported a systolic pressure of 140^{mm}, and Wolf and Thacher of $142\text{-}128^{mm}$. All of these figures probably represent the maximum, rather than the average, for in the great majority of cases, the pressure is known to fall much below these readings, especially in the advanced disease, where a systolic pressure of $60\text{-}80^{mm}$ is commonly observed. In one case observed by the writer the systolic pressure fell to 45^{mm} in the late stages. Other observers have reported a systolic pressure as low as 30^{mm}.

The temperature is almost always found subnormal. A hypothermia is the rule in the early stages of the disease, but in advanced cases, especially in the presence of complications (tuberculosis), the disease may run a febrile course. Hyperpyrexia at times occurs.

The skin usually shows no important characteristic changes, apart from the melanoderma. As a rule, it is soft and elastic, in contrast to the dry and shrivelled skin of other chronic wasting diseases. Excessive sweating sometimes occurs. A disagreeable fish-like odor of the skin has been described (Neusser), and also (with extreme emaciation) a cadaveric odor (Rolleston).

The symptoms referable to the genitalia consist mainly in amenorrhea and menstrual disorders in women and impotence in men. Falta(*c*) has observed that atrophy of the gonads is almost always present. Not infrequently the genitalia may become invaded by the general tuberculous or carcinomatous process. In women carcinoma of the uterus and ovaries, and in men tuberculosis of the epididymis are commonly observed.

There are frequent variations from the type of the disease, arising from the absence, or the preponderance, of one or more of the cardinal symptoms, or from the presence of a predominant complication. Such atypical cases (*formes frustes*) may render the diagnosis a matter of much difficulty. The asthenia is rarely absent, but cases, quite frequently, run their course with a complete absence of the melanoderma. In other instances the gastro-intestinal disturbances are wanting. Again, the sequence of the symptoms may show an unusually wide variation, and one or more of the cardinal symptoms may become only imperfectly developed, or appear late in the disease. The frequently occurring complications (tuberculosis, carcinoma), when of a severe grade, may cause a marked deviation from the type, and, at times, almost mask the Addisonian syndrome. The milder forms of tuberculous foci, commonly localized elsewhere in the body, do not, ordinarily, modify greatly the cardinal symptoms, but the more severe lesions (pulmonary, intestinal, peritoneal, men-

ingeal or miliary) may entirely dominate the clinical picture, and obscure the essential features of the symptom-complex.

The Blood.—Although Addison first regarded this disease as an idiopathic anemia, the blood examination in the majority of patients shows the erythrocytes to be within fairly normal limits, or only slightly reduced. In some patients, a pallor of the skin, associated with the characteristic bronzing, simulates the appearance of a primary anemia. According to Nothnagel(*b*) anemia is not an integral part of Addison's disease. In the advanced cases, however, complicated with tuberculous or cancerous lesions, or severe gastro-intestinal disorders, a marked secondary anemia may be found. In the average patient the erythrocytes rarely fall below 3,000,000, and in some rare instances a polycythemia has been reported with red counts of over 6,000,000. From a series of hospital records, an average erythrocyte count of 4,500,000 was determined. The hemoglobin content was found to average 84 per cent (Sahli), and the leucocyte count 10,000. Several observers have remarked that the hemoglobin content is relatively low in the greater number of cases. The abnormally high erythrocyte count observed by some writers is probably due to the concentration of the blood, subsequent to a profuse diarrhea.

The leucocyte formula has shown, in some instances, interesting deviations from the normal. Neusser has called attention to the relative frequency of a lymphocytosis, an observation that has been confirmed by a number of writers. Another important observation is the somewhat common finding of an unexplained eosinophilia. In Wolf and Thacher's case an eosinophilia of 20.5 per cent was determined. The polymorphonuclear cells are frequently found decreased, in some cases falling below the total lymphocyte count. In one case reported the polynuclear cells were found to be as low as 36 per cent. Marañón, in a study of the leucocytes in Addison's disease, observed, in his series, a mononucleosis of from 35-60 per cent. Neusser regards the presence of a lymphocytosis as an unfavorable sign. The possible relation of these changes in the leucocyte formula (lymphocytosis, eosinophilia, neutrophilopenia) to *status thymicolymphaticus* in Addison's disease, merits further study.

Urine.—The urine, as a rule, shows few important changes. The total quantity is usually decreased, although polyuria, sometimes associated with polydipsia and polyphagia, has been noted in a few examples. The specific gravity may be somewhat low. The coloring matter is not present in excess in most cases; indeed, some writers state that the urinary pigments are actually diminished. An excess of indican is commonly observed. A large number of reports would seem to indicate that the principal urinary constituents are present, in the majority of cases, in normal proportions. There are in the literature, however, isolated observations of the finding of abnormal bodies. McMunn described an increase in urinary pigments, and in one case, the presence of an abnormal color-

ing matter (urohematoporphyrin), determined spectroscopically. Such findings as taurocholic and hippuric acids (Leva), and of increased volatile fatty acids (Gerhardt and Reichardt), and of the appearance of certain amino-acids (Ewald), have not received general confirmation. Wolf and Thacher found an absence of creatin in one case. In a single instance in which the renal function test (phenolsulphonephthalein) was recorded (Daland), normal readings were obtained.

Gastropathy.—The gastric analysis, as a rule, shows no abnormality characteristic of the disease. Hyperacidity has been noted, especially in the earlier stages, while in the advanced stages, the acidity is usually diminished. In a series of cases, in various stages, from hospital records, the free hydrochloric acid reading was found to range from 15-34, and the total acidity from 30-46. An absence of free hydrochloric acid and of pepsin has been observed in only a few instances.

Metabolism.—Owing possibly to the rarity of the disease, comparatively few metabolic studies have been undertaken, and our knowledge of the total metabolism is, as yet, somewhat meager. A loss of weight, of greater or less degree, usually accompanies the disease, but extreme emaciation is rare. The earlier studies of protein metabolism were confined mainly to an investigation of the nitrogen balance, and to an estimation of the effect of the administration of adrenal gland substance on the protein metabolism. According to Richter the protein metabolism is not appreciably altered. Senator's investigations led him to conclude that the administration of the gland substance produced an increase in body weight, and a retention of nitrogen, with a slight calcium loss. But Kaufmann and Pickardt, on the other hand, found an increased nitrogen loss during the administration of the gland substance. Vollbracht and Eiselt have reported an increased phosphoric acid elimination in the disease, which Richter has attempted to explain on the assumption of an increased destruction of bone substance. The investigations of Leva, and of Wolf and Thacher, have adduced some evidence to show that the protein metabolism, especially the endogenous protein metabolism, as indicated by the creatinin and uric acid output, is lower than normal. Wolf and Thacher further observed that the desamidating capacity of the patient and his capacity to transform sulphur into sulphuric acid were absolutely comparable to that of normal persons. Marchetti and Stefanelli have advanced the opinion that the oxidative capacity of the organism is diminished in Addison's disease, basing their theory upon the manner in which the patients react to a diet low in nitrogen and caloric value. Löffler, in a case of Addison's disease, observed a decrease in the used oxygen and in the excreted carbon dioxid, and a low respiratory quotient. There is some evidence to show that a hypoglycemia, and a high sugar tolerance, is characteristic of the disease. Porges and others have reported hypoglycemia in patients with Addison's disease. Eppinger,

Rudinger, and Falta(*c*) have noted a high tolerance for grape sugar, and the absence of glycosuria following epinephrin injection. Mussio-Fournier found a high sugar tolerance in a patient with an atypical form of the disease, in which case glycosuria failed to appear after the ingestion of 200 gm. of glucose, and after the injection of 3 mg. of epinephrin. Schlesinger has confirmed the absence of glycosuria following epinephrin injection. Rutelli has observed that the appearance of glycosuria following epinephrin injection may be considerably delayed in a patient with Addison's disease, as compared with a healthy subject.

Course.—The more typical cases of the disease pursue, almost always, a chronic course, with an average duration of from two to four years. The symptoms progress slowly, and the mode of progress, as Greenhow pointed out, may be paroxysmal, with alternating remissions and exacerbations. During the intermissions the bodily strength may be to some extent restored, with an amelioration of all the symptoms, but following each exacerbation, the symptoms become progressively more severe. Extremely chronic types of the disease have been reported, in which, with the periods of remissions and intermissions, the patients have lived for ten, or as long as twenty, years from the onset of symptoms. The more chronic types are usually associated with an uncomplicated tuberculosis of the suprarenals. The progress of the disease is more rapid, as a rule, in cases due to atrophy of the glands. Not infrequently, chronic cases, running a mild course for a long period, suddenly develop acute symptoms, and terminate fatally within a few days or weeks, or conversely, in rarer instances, the disease may begin acutely, with severe gastro-intestinal disorders, and subside into the chronic type. In the acute form of the disease a very rapid course may be run. In a case reported by Motzfeldt death occurred in two months, and in one reported by Mann (without characteristic symptoms) in four weeks. Sergent and Bernard, as well as Tieken, have described cases in which a fatal ending occurred in ten days from the time of onset of acute symptoms. Karakascheff has reported a still more rapid case, the patient dying within five days, due to a thrombosis of one suprarenal, and a recent infarction of the other. The acute cases of the disease have usually been found associated with destruction of the glands by hemorrhage, or thrombosis, and one or more of the cardinal symptoms are frequently wanting, especially the pigmentation, although the gastro-intestinal symptoms may be acute. Some of the acute cases reported in the literature, under the caption Addison's disease, might more properly be classified as cases of acute hypoadrenia. In children the disease commonly runs a rapid course with severe gastro-intestinal symptoms. In any type of the disease death may occur suddenly, from a syncopal attack, or from exhaustion following uncontrollable vomiting or diarrhea. In the chronic type the fatal termination may come slowly and gradually, usually accompanied, or preceded by, more or

less delirium, from which the patient lapses into a stupor or deep coma.

Diagnosis.—The diagnosis is readily established in the typical case, in which the cardinal symptoms—asthenia, digestive disorders, and pigmentation—are outspoken. In the atypical cases (*formes frustes*) with absence of one or more of these symptoms, a positive diagnosis is sometimes rendered impossible during the life of the patient. Cases of the disease, without melanoderma, are known to occur, but are probably less common than the older statistics would indicate. In such instances the diagnosis is extremely difficult and the disease may pass unrecognized. In these atypical forms Barker(*a*) has emphasized the importance of noting: (1) the presence of constitutional anomalies corresponding to *status thymicolymphaticus;* (2) exact studies of the pigmentation of the body; (3) careful analysis of any digestive disturbance present.

The critical survey of the anamnesis is of equal importance with the physical examination in arriving at a proper diagnosis of the disease. If there can be obtained a history of progressive weakness, gastro-intestinal disturbances (nausea, vomiting, gastralgia, constipation or diarrhea), and of neuralgic pains localized in the lumbar region, or in the abdomen, from a patient, in whom the physical examination shows pigmenting of the skin and of the mucous membranes, and an absence of any organic disease of the viscera, or of a blood dyscrasia, a positive diagnosis of Addison's disease may be regarded as well substantiated.

Pigmentation of the skin occurs in many other pathological conditions, but is rarely so pronounced as in the extreme Addisonian melanoderma. It is the less severe grades of pigmentation which give rise to difficulty in diagnosis. The more important pathological states, in which increased pigment deposit may occur and from which the Addisonian pigmentation must be differentiated, are:

(1) Hemochromatosis (glycosuria, enlarged liver, absence of marked asthenia: pigment contains iron).
(2) Argyria (pigmentation slate colored: history of silver nitrate medication).
(3) Arsenical pigmentation (usually history of prolonged arsenical medication: hypertrophic processes in the epidermis).
(4) Pernicious anemia (color of skin usually lemon colored, but pigmentation here may be due to prolonged taking of arsenic: mucous membranes not pigmented: blood examination).
(5) Pellagra (seasonal appearance of a rash: marked asthenia absent).
(6) Jaundice (icterus of scleræ: bile in urine: history of cholelithiasis, or obstruction from a mass).
(7) Cachexias, accompanying tuberculosis, carcinoma, malaria,

syphilis and arthritis deformans. In both tuberculosis and carcinoma the chromaphil tissue may be involved but the asthenia is rarely so extreme as in Addison's disease. In malaria (history: finding of plasmodia in the blood: enlarged spleen): syphilis (history: Wassermann): arthritis deformans (characteristic joint changes).

(8) Certain skin diseases; vagabond's disease; chronic eczema, scleroderma, melanosarcoma of the skin, vitiligo, xeroderma pigmentosum (absence of cardinal symptoms).

(9) Neoplasms, especially abdominal forms: melanotic carcinoma, melanosarcoma, lymphoma; benign tumors of the uterus and ovaries; pseudoleukemia; neurofibromatosis, in which diffuse bronzing and pigmentation of the mucous membranes may occur (subcutaneous nodules).

(10) Exophthalmic goiter (symptoms of hyperthyroidism). In rare instances the two diseases may be associated in the same patient.

(11) Pregnancy (pigmentation usually limited to the face: tumor).

(12) Gastric disease—gastric ulcer and dilatation of the stomach are sometimes accompanied by a pigmentation of advanced grade (gastric findings: radiogram).

(13) Cardiovascular disease—arteriosclerosis, chronic heart disease, and chronic interstitial nephritis, may at times show pigmentation (physical examination: blood pressure: electrocardiogram: urinalysis).

The presence or absence of an asthenia is regarded by many authorities as the most important factor for consideration in establishing the diagnosis. In the absence of this symptom in a patient with melanoderma, in whom other possible causes for the pigmentation have been excluded, it is believed that a diagnosis of Addison's disease should only be tentatively rendered, until such time as this symptom develops.

The pigmentation of the mucous membranes is a further valuable diagnostic aid, but is not pathognomonic of this disease. It occurs physiologically in some races, negroes and certain yellow races (Japanese), and also occasionally in such pathological states as chronic stomach disease, and neurofibromatosis. Further, it is sometimes absent in Addison's disease.

In every suspected case, an examination of the patient for the presence of lymphatic anomalies associated with *status lymphaticus* should be carefully made, since Wiesel(*e*) and Hedinger have shown this condition to bear a close relation to hypofunction of the chromaphil system. Neusser has called attention to the great difficulty of making a diagnosis of *status lymphaticus intra vitam*, but the finding of enlarged tonsils, enlarged

lymph follicles at the base of the tongue, hyperplasia of the entire pharyngeal ring, lymphoid growth in the nose, enlarged lymph glands in the cervical, axillary and inguinal regions, enlarged spleen, persistent thymus, together with anomalies of the genitalia and of the secondary sexual characteristics, and of the distribution of body hair, constitutes corroborating evidence of the possible presence of this condition. A study of the blood picture may also prove of value since a mononucleosis with an absolute reduction of the neutrophilic leucocytes, and occasionally an eosinophilia, may occur in status thymicolymphaticus.

We have, as yet, no reliable test for hypofunction of the suprarenal glands, but a few suggestions have been made concerning procedures to determine the presence of suprarenal deficiency in the suspected cases of the disease. Grünbaum has advocated the use of suprarenal extract as a diagnostic aid. According to this writer, in cases of hypotension, the administration of 3 grains of the extract for three days will cause a rise in blood pressure. If a rise of more that 10^{mm} is found, he regards it as good evidence that a case of hypotension with pigmentation is one of genuine Addison's disease. Other writers have advised the study of the blood-sugar content since there is some evidence to show that a hypoglycemia exists in this disease. The estimation of the sugar tolerance, and the determination of the absence or the presence of a glycosuria, following epinephrin injection may throw light upon obscure cases in the future. Several observations seem to indicate that a high sugar tolerance, and an absence of glycosuria after epinephrin injection, are characteristic features of the disease. Since the lesion in the suprarenals is most commonly tubercular, the tuberculin test has been frequently employed as a diagnostic measure. Either the ophthalmic, cutaneous, or subcutaneous tests may be used, but with a positive reaction, the probability of tuberculous foci in other parts of the body must be considered, and it should be recalled that the subcutaneous injection of tuberculin has occasionally evoked alarming symptoms in patients with Addison's disease.

The vasomotor skin reflex, or "white line" (ligne blanche surrénale) of Sergent(*b*) is found present in many patients with Addison's disease, and should be looked for in all suspected cases. The test is made by stroking the skin, preferably of the abdomen, with a blunt object, or simply the finger tip. After about half a minute, a pale line or band appears, gradually becoming more distinct and persisting for from 1-3 minutes. According to Sergent this phenomenon indicates a suprarenal insufficiency, but other observers attribute to its presence only a relative diagnostic importance, regarding it as by no means pathognomonic of this condition.

While our present diagnostic armamentarium is sufficiently developed to permit the making of a clinical diagnosis of Addison's disease in a patient, especially in the outspoken cases, our methods of investigation are

as yet too crude to enable us, except in rare instances, to establish an exact diagnosis *intra vitam* of the underlying etiological factor, or of the anatomical changes present in the suprarenal glands (interrenal and chromaphil systems).

Prognosis.—The prognosis is always unfavorable, death usually occurring within from two to four years following the onset of symptoms. Instances of recovery have, however, been rather commonly reported. In cases that begin insidiously with mild symptoms, the disease may be protracted for ten or fifteen years, especially when associated with an uncomplicated suprarenal tuberculosis, but the prognosis must always be guarded, since death may occur at any time during a syncopal attack, or the disease become transformed into an acute type, leading to a speedy termination, at any stage of its course. According to Elsner the prognosis is apt to be better, so far as length of life is concerned, in proportion to the extent of the pigment deposit, chronic cases usually showing the greatest pigmentation. Unfavorable symptoms include progressive emaciation, marked hypothermia, persistent hypotension, severe diarrhea, anemia, large mononuclear lymphocytosis; hypoglycemia, and a high sugar tolerance; intermittent hypothermia and pyrexia; the development of mania or melancholia. The presence of a normal blood pressure and of a normal blood-sugar content are regarded as favorable signs. Schlesinger believes that epinephrin injections may prove helpful in making a prognosis. He states that if the blood pressure shows no rise following such injections, death may be expected at an early period. Similarly, Massalongo regards the anemic vasomotor skin reflex (ligne blanche surrénale of Sergent) as having some prognostic value, since its maximum frequency is met with in cases of serious import.

In many of the cases of recovery reported in the literature, considerable doubt has been entertained in regard to the correctness of the diagnosis. Several of these cases have probably been syphilitic in origin. A number of cases have been reported as cured following suprarenal therapy. It is well established that such treatment may often produce a temporary amelioration of the symptoms, but in all such reports, the possibility of the usual occurrence of remission and intermissions of the symptoms, without such therapy, should be considered. Bittorf(*a*) has described cures in cases associated with hypernephroma, and Oestreich operative cure of a tuberculous suprarenal with tumor formation. Tieken has recently reported a cure in a case, which was regarded as due to the interference of suprarenal function by an inflammatory exudate extending from the pelvis of the kidneys. It is, perhaps, significant that the great majority of reported cures have occurred in cases in which the diagnosis has been open to doubt, or in which some etiological factor, other than the common one, tuberculous caseation of the suprarenals, has been present. Kraus believes that all cases of tubercular origin terminate fatally. Other observers are

of the opinion that recovery is conceivable, in tuberculous cases, if the primary lesion in the suprarenal heals, and sufficient intact cortical tissue, and extra-suprarenal chromaphil tissue, remain to carry on the function of the gland.

Treatment.—The high mortality in this disease affords a criterion of the inefficacy of any form of therapy yet devised. Following Addison's discovery of a destructive lesion of the suprarenal glands as the causative factor, clinicians attempted to effect a so-called "causal" or "substitution" therapy, with the hope of replacing the perverted function of the glands. Two possible methods of attaining this appeared rational, either the grafting of healthy suprarenal glands into the tissues of the patient, or the administration of the gland substance itself. Unfortunately, neither form of substitution therapy has as yet proven efficacious. It has not been possible, so far, to produce a functioning suprarenal graft in man, and while a certain number of cures have been reported, following the use of suprarenal gland substance, this method of treatment has in no measure yielded the brilliant results obtained by the administration of thyroid extract in *cachexia thyreopriva.*

The problem of a glandular therapy in Addison's disease is beset with many difficulties, in the fact that very rarely are we dealing with the condition of a purely functional disturbance of the suprarenal glands. Associated with the hypofunction are pathological changes in the gland substance and adjacent tissues (sympathetic nervous system and extramedullary chromaphil tissue), the nature and extent of which cannot be determined. A further obstacle lies in our imperfect knowledge of the function of the suprarenal gland as a whole, or of its component parts (interrenal and chromaphil systems). Indeed, modern physiological investigations have not adduced any reliable evidence of the presence in the blood of any secretion of the suprarenal glands under ordinary peaceful conditions of life. It is evident, that for the present, any form of suprarenal therapy must remain purely empirical.

The literature of Addison's disease has, however, become filled with the records of experiences with suprarenal gland therapy. The evidence is conflicting, and frequently misleading, since an impartial judgment of the final result is rendered difficult by the fact that remissions are of common occurrence in the disease, in the absence of any therapeutic measure. In general, failure has been more commonly reported than benefit from this form of therapy. A number of writers have endeavoured to explain these numerous failures. Bramwell has assumed, in such cases, an involvement of the sympathetic system by adhesions and irritation. The cases which improve on suprarenal treatment, he believes, are those in which only a glandular inadequacy is present. Shaw describes the difficulty of securing an adequate absorption of epinephrin as a possible cause of failure. Sajous(*a*) regards the unfavorable results obtained as due in a

great measure to an empirical use of the extract, regardless of the dosage indicated in each case. Schafer(*a*) has pointed out that the administration of the gland extract cannot, as in the case of *cachexia thyreopriva,* take the place of the internal secretion of the gland, and expresses the opinion that until measures are found to induce grafts to take in man, Addison's disease will probably continue to terminate fatally. Timme has recently stated his belief that the terminal types of endocrin disturbances, such as Addison's disease, are largely beyond the reach of glandular therapy.

In only a few instances have attempts been made to replace the function of the diseased glands by the transplantation of healthy suprarenals into the tissues of patients with Addison's disease, and in such cases the results have been uniformly unsuccessful, and mainly disastrous. Bra transplanted the suprarenals of a dog into the cellular tissue of the abdomen, in the case of a child with Addison's disease, but the operation was followed by death in three days. Jaboulay reported two cases, with death within twenty-four hours, following suprarenal transplantation. Courmont, after a similar operation, described a "formidable hyperthermia," without infection of the wound, and a cardiac collapse, in his patient, followed by death in twenty-four hours. As a result of his experience he regarded this form of therapy clearly contraindicated in Addison's disease. The results of animal experimentation have, moreover, proven a deterrent towards such procedures in the human subject. Canalis, the first to attempt suprarenal transplanting in animals, grafted small portions of the gland into the kidney, but found that in every case except one, the grafts became necrotic and were absorbed. Gourfein, Abelous, Boinet and others have also reported unsuccessful results from grafts in various parts of the body. Stilling(*d*), after grafting the suprarenals into the testes, was able to find cortical tissue as late as three years following the operation. One of the most successful attempts recorded is that of Busch, Leonard and Wright, who were able to transplant the suprarenal of one rabbit into the kidney of another, and to obtain positive evidence of functioning graft survival, with a preservation of the medullary tissue of the grafted gland. These authors believe the kidney to be the structure best adapted for the reception of the grafts. With the progress of surgery the hope of a successful form of substitution therapy in Addison's disease, by suprarenal grafting, appears more rational than formerly.

The reports in the literature, by competent observers, of the beneficial results derived from suprarenal gland therapy have become sufficiently frequent to merit consideration. The improvement recorded has been mainly in the direction of diminishing the asthenia. Langlois(*c*), one of the first to employ this form of treatment, believed that the myasthenia could be markedly decreased, basing his view upon the ability of a patient, thus treated for a period of six weeks, to lift a weight 5-8 times longer than before treatment, as demonstrated by ergographic tests. In

Adams' series of 97 cases, improvement was observed in 33 instances and permanent relief (cure?) in 16. Sajous(*a*) has supplemented this series to include 120 cases, noting marked improvement in 36 cases, and permanent benefit in 25. These results have been contrasted with the figures of Lewin, who had previously reported a series of 800 cases treated by methods other than suprarenal therapy, with instances of improvement in only 28 cases and of cure in 5. Several observers have recorded a decrease in the pigmentation following glandular therapy, an effect which has been contrasted with the observing of a rapid return of the bronzing, in some instances, when gland therapy was stopped. In a case reported by Osler, the pigmentation cleared up, along with the other symptoms, the patient dying subsequently from an acute infection, not apparently associated with the suprarenal disease. Other observers have described a gain in weight following suprarenal gland administration, Weigall recording a gain of 56 pounds in about three months, but the metabolic studies of Pickardt and Kaufmann have demonstrated an increased nitrogen loss following such therapy. Quincke has recently reported two cases of cure in patients with Addison's disease, by the administration of suprarenal glands, and has suggested that in these patients a diminished function of the glands, without anatomical lesions, the result of undernourishment, and faulty environment during the war, was the probable etiological factor. In the purely functional types of Addison's disease a beneficial result from glandular therapy is quite readily conceivable. Unfortunately such instances are rare.

Various preparations of the suprarenal glands from different animals were employed by the earlier clinicians in this form of therapy, including the fresh glands, aqueous or glycerin extracts of the glands, tinctures, partially cooked, or desiccated glands. The suprarenals of the sheep have been most commonly used. The mode of administration, at first, was by subcutaneous injection, but following the observation of Oliver and Schäfer, that the activity of the gland was not destroyed by hydrochloric acid and pepsin *in vitro* oral administration, became quite general. More recently, with the discovery of the active principle of the medulla by Oliver and Schäfer(*a*), and the isolation of the same by Takamine(*a*), clinicians have frequently used this purified active principle (epinephrin) in preference to the administration of the extract of the whole gland, some authorities considering it more correct physiologically to administer a substance of known strength. It has been employed both orally and hypodermically, but the results obtained have proven even less encouraging than with the use of the whole gland extract.

As a result of animal experimentation, a considerable number of data have been obtained concerning the pharmacological action of the gland substance, and of the active principle. Foà and Pellacani, among the earlier investigators, succeeded in producing death in a day in animals,

by the use of a strongly concentrated aqueous solution. Alezais and Arnaud, however, as a result of their experiments believed that the fresh gland substance contained no toxic principle. Vincent(*f*) observed, following the subcutaneous injection of sufficiently large doses of suprarenal extract, slowed muscular movements, paresis, and finally paralysis of the limbs, bleeding from the mouth and nostrils, hematuria, respiratory disturbance, and occasionally convulsions preceding death, before which the temperature often fell very low. This author regarded the paralysis as central, and the effects as due to the medulla of the gland, the cortex containing no toxic substance. He further noted that the oral administration of the glands in animals gave rise to no noticeable physiological effects. Blum(*b*) first made the important observation that glycosuria can be produced by the subcutaneous or intravenous injection of suprarenal extracts into animals.

Several important observations concerning the physiological action of epinephrin have a bearing upon the therapeautic indication for the use of this drug in the treatment of Addison's disease. Here it may be stated that there is good evidence to believe that the chromaphil tissue, outside of the suprarenal medulla, contains an active principle identical in its physiological action with the epinephrin of the medulla (MacLeod). The first and most important observation was that of Oliver and Schäfer of a rise in the blood pressure, which they regarded as due to a constriction of the arterioles, as well as to an increase in the rate and energy of the heart beat, i. e., the maintenance of vascular tone. But Moore and Purinton first noted that very small doses of suprarenal extract cause a fall in blood pressure, an observation that has been confirmed by several observers. Hoskins has demonstrated by animal experimentation, that the quantity of epinephrin required to produce a minimal hypertension is several times (10-20) the amount normally secreted by the suprarenal glands. Another important observation is that of Elliott(*a*) who found that the injection of epinephrin caused identically the same effects as the stimulation of the sympathetic (thoracico-lumbar autonomic) nervous system, the injection affecting all structures innervated by sympathetic fibers. Following epinephrin injection either stimulation or depression may be produced in a structure, according to the rôle of the sympathetic fibers. Among other physiological actions described, of interest in this connection, are: a redistribution of blood in the body, vasoconstriction in the skin and splanchnic areas, and vasodilatation in the skeletal and heart muscles, lungs, and central nervous system (Cannon); the production of hyperglycemia, and of glycosuria; increase in body temperature, increase in the lymphocytes and polynuclear leucocytes, and in the erythrocytes in the blood. In general, as Hoskins has pointed out, epinephrin is neither a vasoconstricting nor a vasodilating agent in any broad sense, but is either one or the other depending on the vessels involved. Furthermore,

in some instances, the action varies with the dosage. Another fact, which the physiologists have recently demonstrated, and which should be borne in mind in the efforts of clinicians to effect a "casual" therapy, is that a true epinephrinemia probably never exists under ordinary conditions, and that the suprarenal deficiency in this disease is not, so far as we know, dependent upon an epinephrin deficiency. In our present lack of knowledge, therefore, it would appear more rational to administer the whole gland substance rather than epinephrin in the treatment of the disease (Vincent(*g*)). Until our information concerning the function of the glands, and the pathogenesis of the disease, becomes more exact, the treatment by means of the gland substance must remain purely empirical, but that such therapy is legitimate, and should be attempted in every case, is the opinion of most authorities.

The preparation most commonly used at present is the desiccated gland substance (*Glandul suprarenales siccæ*, U. S. P.), prepared from the suprarenals of the sheep, in powdered or tablet form, one grain representing approximately five grains of the fresh gland. The average official dosage is about 5 grains (0.32 gm.) thrice daily, given orally, but the information concerning the optimum dosage in the treatment of Addison's disease is meager. Good results have been reported from both smaller and larger doses than the average. Bate recorded great improvement with the administration of 1/12 of a grain (0.005 gm.) thrice daily while Daland observed the best results to follow a dosage of 35 grains (2.2 gm) thrice daily. Sajous(*a*) believes that the temperature and blood pressure readings may afford an index of the optimum dose in the individual case, and that the aim in treatment should be to adjust the dosage to the needs of the organism. This author advises the use of 3 grains (0.2 gm.) thrice daily, if the blood pressure and temperature are considerably below normal, increasing the dose if necessary until the pressure and temperature become normal, and regulating the dose, thereafter, to maintain this level. Some observers maintain that the oral administration of large doses of the extract fails to produce any noticeable rise of blood pressure, but Grünbaum states that although such failure usually occurs in normal subjects, in patients with Addison's disease, an elevation of the blood pressure may be produced by oral administration. It should be recalled that untoward effects have sometimes followed the therapeutic use of the gland extract. Adams mentions an alarming collapse in two patients treated by Affleck with suprarenal gland extract. Boinet(*h*) observed marked excitement, tremor and insomnia in a patient treated with a glycerin extract of the whole gland. Daland found that toxic doses of the extract (90 grs. t.i.d.) produced mental and physical weakness, irritability and insomnia, which disappeared when the dose was diminished. Death was attributed to the use of gland preparations in several instances in Adams' series.

Epinephrin is usually administered hypodermically, from 5-10 minims

of the 1:1000 solution. Some authorities have advised the giving of epinephrin by mouth, but such oral administration is mainly ineffective, as much as 20 mgm. a day causing no special manifestations (Vincent(*f*)). A few observers have reported beneficial results from the use of the drug in Addison's disease but frequent warnings have been made against the use of large doses. The prolonged usage of epinephrin in the treatment of the disease is strongly contraindicated, especially in advanced cases, and in aged individuals with arterial changes. Boinet(*i*) has reported sudden death in two patients following the injection of small doses. Daland observed cardiac dilatation following toxic doses. It is believed that suprarenal apoplexy may be the cause of death, at times, following epinephrin injection. Arnstein and Schlesinger have recently warned against the use of the drug in elderly persons, having observed that in such individuals, following a small dose, the initial rise of blood pressure is followed by a sharp fall and a slowing of the pulse; also that in the presence of coronary sclerosis, severe attacks of stenocardia may be produced. Elliott regards the unfavorable symptoms, at times produced, as mainly due to poisoning of the tissues by quantities of epinephrin exceeding that sufficient for physiological stimulation.

The general conclusions which may be derived from reports of glandular therapy, in this disease, are that only in the earlier stages may any marked degree of improvement be expected, and that in the later stages no beneficial result is likely to occur; further, that in the advanced cases great care should be exercised in the administration of either the gland substance or of the active principle.

Quite recently some observers have advocated the use of pituitrin, in conjunction with epinephrin, on account of its pressor effect. The reports, so far, do not indicate that such combination of pressor principles is of greater therapeutic value than the administration of epinephrin alone.

Some consideration has been given by clinicians to the feasibility of a surgical treatment of the disease, by extirpation of the diseased gland. Cure, in such a manner, has been reported by Oestreich, who removed a tuberculous tumor of the suprarenal. The syndrome of the disease was incomplete in his case, however, and many observers have doubted the diagnosis. There appears to be no authentic instance of recovery following operative treatment in genuine cases of Addison's disease. In forms of the disease in which a tumor can be recognized exploratory operative procedure is doubtless justifiable. Almost always, however, the lesion in the suprarenal in this disease is bilateral and extirpation of both glands is known to be invariably fatal. Furthermore, as Wiesel(*d*) has demonstrated, the extramedullary chromaphil tissue is commonly involved. Both of these factors are serious obstacles towards any successful operative form of treatment.

Owing to the frequency of tuberculous lesions in the suprarenals in this disease a few clinicians have attempted to treat the condition by tuberculin injections. Beneficial results have been recorded by a few observers. Brünecke has recently noted a marked improvement following the use of partial antigens in a case of acute Addison's disease following influenza. Experience has shown, however, that the use of tuberculin in Addison's disease is at times followed by alarming symptoms, which, it has been suggested, may be due to a local reaction in the region of the suprarenals, resulting in acute insufficiency of the glands. It is obvious that if tuberculin be employed therapeutically, it should be administered with caution. In other rare cases of the disease syphilitic lesions have been found in the glands, and in cases of Addison's disease, in which the Wassermann reaction is positive, anti-luetic treatment is indicated.

It seems not improbable that future metabolic studies in this disease may enable the clinician to influence the course of the disease by dietetic measures. Some attempts have already been made in that direction following the observation of the low glycogen of the liver in animals deprived of their suprarenals, as well as of the presence of a hypoglycemia in patients with Addison's disease. Porges has observed favorable results, by increasing the carbohydrates (especially of levulose) of the diet, in a number of patients. Grote treated a case with suprarenal extract and the administration of 100 gms. of sugar daily, noting a rapid improvement, gain in weight, disappearance of the pigmentation of the skin, and a rise in the blood sugar content. Pitres and Gautrelet also found the use of glucose to be followed by a material improvement in the asthenia.

Sooner or later in the disease, apart from any efforts to influence the course by glandular therapy, symptomatic treatment becomes imperative. Due to the fact that tuberculosis is so frequent a concomitant of the disease, both in the suprarenal glands and in other foci in the body, with pulmonary lesions present in a large proportion of the cases, the advocacy of a general anti-tuberculous régime of treatment is well founded. Especially should the importance of rest, even in the early stages, be impressed upon the patient, and the avoidance of undue physical exertion, since instances of sudden death have been known to follow severe effort. Boinet reported seven such cases. In acute forms of the disease, and in all advanced cases, absolute rest in bed is necessary, and, indeed, usually obligatory, the patient becoming unable to rise. In such cases, prolonged examination by the attending physician should be avoided. The gastro-intestinal disturbances often prove troublesome. The nausea and vomiting may frequently be relieved by gastric lavage. Constipation should, if possible, be avoided by dietetic measures, or only the mildest laxatives employed. The use of drastic cathartics in this disease is strongly contraindicated, since fatal collapse has not infrequently followed such purging, a fact to which Greenhow first called attention. For controlling diarrhea

large doses of bismuth, as well as dietetic measures, have been advised. Cardiac stimulants, such as camphor, ether, or digitalis, have been recommended for the cardiac weakness, especially in the later stages of the disease. Some observers have advised the administration of iron, arsenic and strychnin to combat the debility. A remission of the symptoms has been observed by some writers following the use of arsenic. For the coma which precedes the *exitus lethalis* in a large proportion of the cases, all remedial measures attempted have proven futile.

Clinical Syndromes . . . . . *Benson A. Cohoe*
Hypoadrenia—Conclusion.

Clinical Syndromes due to Suprarenal Diseases

Hypoadrenia

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The growing interest in diseases of the endocrin organs, during the past quarter of a century, has stimulated clinicians in an endeavor to recognize the clinical manifestations of states of altered function of the suprarenal glands. The limitation of our knowledge of the function of these bodies has served to render this task especially difficult. In the opinion of certain physiologists, this knowledge is as yet too meager to justify clinicians in diagnosing any syndromes due to states of overfunction or underfunction of the glands. A similar view has been shared by several clinical authorities, who have pointed out a further obstacle, in that any specific and characteristic symptoms, due to impairment or loss of function, are wanting, as evidenced by the fact that autopsy records have repeatedly demonstrated that extensive pathological alterations in the suprarenal glands may occur in the entire absence of any symptoms during life, suggestive of suprarenal involvement. It may be recalled that Leube, in his work on diagnosis, dismisses the subject with the statement that diseases of the suprarenal glands are incapable of diagnosis. In a recent critique Stewart(*y*) (1921) comes to the conclusion that the conception of hypoadrenia, in the usual sense of the term, has but very precarious scientific standing.

The clinical phenomena associated with a state of underfunction of the gland have been more carefully studied than those of overfunction. The French clinicians have been especially aggressive in their efforts to elaborate a syndrome arising from deficiency of adrenal secretion, and occurring apart from the Addisonian form of adrenal disease. Sergent and Bernard (1899) were among the first to classify a symptomatology of this nature. Various terms have been employed in the literature, descriptive of this condition of underfunction of the gland, including such designations as suprarenal (or adrenal) insufficiency, suprarenal (or

adrenal) deficiency, hypoadrenalism, hypoepinephry, and hypoadrenia. Sajous(*a*) regards the term hypoadrenia as preferable to the more generally used hypoadrenalism, in that the latter term is misleading as conveying the impression of an habitual insufficiency of the gland. The term hypoadrenia appears to have become well established in the literature.

The first step in the recognition of a clinical syndrome associated with arrested function of the gland was rendered possible by the observation on the part of physiologists and pathologists of certain clinical phenomena following suprarenal extirpation in animals, or the production of lesions in the gland substance by means of mechanical injury, or by the injection of certain bacterial and chemical toxins. Brown-Séquard(*a*) first established the vital importance of the organs. Among the symptoms produced by extirpation, he noted muscular weakness, convulsions, delirium and coma.

Hultgren and Andersson made a careful study of the symptoms produced by extirpation. They noted that no ill effects were apparent, except loss of appetite, during the first few days following the operation, but that shortly before death the animals became stupid and apathetic, the temperature fell, and the prostration became extreme. Cardiac weakness, dyspnea, and occasionally convulsions, were also observed. Strehl and Weiss found, in addition to muscular weakness and a low temperature, a fall in blood pressure following extirpation, an observation which was confirmed by Moore and Purinton(*c*) and others. Gastro-intestinal disturbances have also been described by several observers. A loss of appetite was commonly noted, and in some instances increased peristalsis and diarrhea (Nothnagel(*b*), Tizzoni).

Various theories have been advanced as to the cause of death following extirpation of the glands. Alezais and Arnaud, as a result of animal experimentation, concluded that the suprarenal glands, though still functioning in the adult, are not indispensable for life, and that a lesion of the gland may cause death by affecting the nervous system. Abelous and Langlois (*d*) observed toxic symptoms resembling those of curare poisoning (a progressive paralysis beginning in the hind limbs and becoming general before death), after the destruction of the adrenals of frogs by cauterization. They believed that death resulted from the accumulation of toxic substances in the blood, which the adrenal glands normally remove. Battelli(*c*), from a special study of circulatory conditions following extirpation, regarded cardiac failure as the cause of death. With the discovery of the internal secretion of the gland (epinephrin), it appeared plausible to explain the fatal effects of suprarenal extirpation on the basis of epinephrin deficiency in the circulating blood. Elliott(*a*), having demonstrated that the effect of epinephrin injection is exactly equivalent to stimulation of the sympathetic nervous system, has suggested that suprarenal deficiency results from the loss of some substance necessary to maintain

sympathetic irritability, i. e., that epinephrin is of importance in the metabolism of the sympathetic nervous system, particularly of the myoneural "receptive substance." Hoskins and Wheelon(*b*), however, were unable to find any evidence to show that the sympathetic system suffered primarily in any degree from suprarenal extirpation. There is no satisfactory evidence of an experimental nature for the belief that epinephrin deficiency is the cause of death following extirpation. It seems probable that death is due to a loss of the cortical, rather than the chromaphil tissue of the gland.

Destructive lesions of the glands have frequently been experimentally produced by the injection of various toxins, either bacterial (diphtheria, tetanus, pneumococcus, streptococcus, etc.) or chemical (arsenic, mercury, lead, etc.). The first result of such injections is usually the production of hyperemia of the gland, which some authors regard as indicating a state of hyperfunction. If the intoxication is severe, however, an arrested function of the gland results, due to the destructive lesions produced (hemorrhage, softening or necrosis), with the clinical symptoms of hypofunction. Schur and Wiesel(*b*) have observed that prolonged narcosis with chloroform, or ether, in rabbits, may cause the disappearance of the chromaphil substance of the medulla, followed by a rapid return to a normal content in a few hours. Graham was able to produce necrotic lesions in the cortex by chloroform, dichlormethane, and tetrachlormethane, inhalations in animals; also less extensive lesions by the subcutaneous injection of phenol. His observations led him to believe that the suprarenal cortex is very sensitive to poisons, and its cells readily injured or destroyed by these, and further that the cortical parenchyma possesses a power of regeneration, when the lesion is removed. Lattes(*b*) has adduced some experimental evidence in support of the view that superficial burns may cause death by inducing suprarenal deficiency. He found that in animals killed 5-7 days after the infliction of a burn, the cortex showed characteristic changes, consisting of hyperemia, accompanied by hemorrhages. The lipoids of the cortex were considerably diminished and the cholesterol esters almost entirely absent. A study of the epinephrin content of the gland, following acute intoxications experimentally produced in dogs, has been made by Sydenstricker, Delatour and Whipple. In this condition they found a low epinephrin index in the glands. After recovery from a sublethal dose it was observed that a rapid rise to a point considerably above the normal might occur. Certain liver poisons, as chloroform, phosphorus and hydrazin, were found to cause a drop in the index to about half the normal.

A classification of the various types of suprarenal deficiency has been attempted by clinicians. The French writers, mainly, have recognized three forms, the acute, the subacute, and the chronic. The acute form is characterized by the severity of the symptoms, and is usually associated with extensive destructive lesions in the gland, terminating fatally, as a

rule, within a few days. In the subacute form the symptoms are less severe and the course may be prolonged for several weeks or months. The chronic type includes atypical cases (*formes frustes*) of Addison's disease, and other chronic forms arising from a purely functional inadequacy of the gland (faulty development). In this country Sajous(*a*), as a result of extensive study of states of hypofunction of the suprarenal glands, has presented the following classification: (1) Functional hypoadrenia, a form in which the glands are functionally deficient, due to faulty development, or debilitating influences, such as fatigue, starvation, old age, etc., in the absence of organic lesions; (2) Progressive hypoadrenia, or Addison's disease, a form in which the function of the glands is progressively impaired by organic lesions; (3) Terminal hypoadrenia, a form occurring as a more or less late complication of infectious diseases and toxemias, owing to exhaustion of the secretory activity of the glands in the earlier stages of the causative disease.

The symptom-complex of the various forms of hypoadrenia varies greatly in the individual cases, a fact which has rendered a satisfactory classification of the types difficult. The acute forms have been somewhat more easily circumscribed, but even in this group there is a wide variation in the symptomatology, and certain types within this group have been described, depending upon the dominant symptoms, such as the pseudo-peritonitic type of Ebstein, and the pseudo-meningitic type of Sergent.

The acute forms of hypoadrenia are characterized by a sudden onset, and run, in the majority of cases, a rapidly fatal course, death ensuing within a few days. The symptom-complex varies with the nature and extent of the pathological changes occurring in the glands, and, in some cases, with the degree of the involvement of the sympathetic nervous system. The symptoms which have been found associated with this condition are, in general, severe pain in the lumbar region, or epigastrium, or other parts of the abdomen, severe gastro-intestinal disturbances, as vomiting, or diarrhea or both, abdominal tenderness, meteorism, marked asthenia, cardiac weakness and feeble pulse, arterial hypotension, hypothermia (sometimes preceded by pyrexia), cold sweats, cyanosis, collapse, convulsions, delirium, coma, exitus. Of all the foregoing symptoms asthenia, in varying degree, is the most constant in occurrence. In many cases a purpuric rash has been noted, a phenomenon which Dudgeon regards as analogous to the melanoderma of the Addisonian syndrome but which the majority of writers attribute to a general visceral hemorrhagic tendency.

The anatomical changes in the suprarenal glands, which have been most commonly found associated with the clinical syndrome of acute hypoadrenia, are mainly hemorrhage into the gland substance, and inflammatory changes (the so-called suprarenalitis), with softening and necrosis.

It is impossible, in the majority of cases, to differentiate these two conditions either clinically or pathologically. Simple hemorrhage has been noted in a few cases, but the inflammatory changes which have been observed are almost always found associated with more or less hemorrhagic extravasation and necrosis. Apart from hemorrhage and inflammation, suppurative processes in the gland substance have been observed in a few cases of acute hypoadrenia.

Suprarenal hemorrhage was first recognized as a clinical entity by Rayer (1837), since which time the condition has been carefully studied. It is known to be a common cause of death in the new born, and instances of sudden death in adults have been often attributed to suprarenal hemorrhage—the so-called suprarenal apoplexy. The rich vascularity of these glands, ranking next to that of the thyroid, would appear to predispose them to hemorrhage. Simple small hemorrhages occur most frequently within the medullary substance of the gland, and if sufficiently small, may cause only slight destruction of the cortex. Multiple small hemorrhages occur mainly in the cortical tissue, rather than in the medulla, and are usually accompanied by more or less necrosis of the cortical cells. Sudden death in acute suprarenal insufficiency is usually associated with hemorrhage into the medulla. The hemorrhage may be single or multiple, and vary greatly in size. In Rayer's case the hemorrhage formed a blood cyst weighing two kilos, and in a case recently reported by Lusk and Brumbaugh, the hematoma extended from the brim of the pelvis to the splenic flexure and was estimated to be formed of about three litres of blood.

Hemorrhage of the suprarenals has been attributed to a manifold variety of causes, including circulatory disturbances, intoxications, infections, trauma, superficial burns, asphyxia, inflammatory or suppurative changes in the gland, hemorrhagic diathesis, convulsions, neoplasm, and hydatid cyst. On account of the rich vascularity it is believed that simple alterations in the blood supply, or a sudden rise in the blood pressure may give rise to hemorrhage in the gland. Dudgeon is of the opinion that any disease which is known to produce stagnation of the blood in the veins, or a marked increase in the blood pressure may be a causative factor of suprarenal hemorrhage. Boinet(*i*) has reported sudden death following the injection of epinephrin in Addison's disease, due to the sudden raising of blood pressure in an already diseased gland. Similarly, paroxysms of coughing, and epileptic convulsions, may produce hemorrhage by a sudden rise in blood pressure. Infectious diseases are frequently accompanied by alterations in the glands, among which alterations hemorrhage and necrosis are commonly found. Trauma has been noted as a factor in only a few instances. Severe superficial burns have been regarded as the cause of hemorrhage in cases reported by Dudgeon and by Arnaud, in both of which instances the clinical symptoms of hypoadrenia appeared before death. More recently, Weiskotten has attributed the changes found

in the suprarenals at autopsy in cases of uncomplicated superficial burns, as due to a specific toxin originating in the burned area, rather than to hemorrhagic infarction as formerly believed. Asphyxia, with the resulting venous engorgement, is considered a common cause of hemorrhage in the new born.

There is no characteristic syndrome associated with suprarenal hemorrhage, whereby it may be differentiated clinically from other types of acute suprarenal insufficiency. Sajous(*a*) has emphasized the point that suprarenal hemorrhage is frequently preceded by a state of hyperactivity of the gland, serving as a defensive mechanism, and resulting in a condition of hyperadrenia. This hyperadrenia he regards as the cause of the hyperpyexia frequently observed in the course of the infectious diseases, preceding suprarenal hemorrhage. In some cases of hemorrhage sudden death may occur without premonitory symptoms. In the majority of cases, however, there is an abrupt onset with intense abdominal pain radiating to the loins, vomiting, profuse diarrhea, tympanites, convulsions and collapse, with death in from 6-48 hours. The condition is frequently mistaken for that of acute hemorrhagic pancreatitis, which it closely resembles. In children, hemorrhagic purpura, or petechial hemorrhages, are commonly present. It is believed that not all cases of suprarenal hemorrhage terminate fatally. Small hemorrhages may form hematoma and give rise to but few symptoms of insufficiency, since the function of the gland is not materially affected (Sajous).

Inflammatory changes in the suprarenals, as has been pointed out by Lavenson, are rarely of the nature of a true epinephritis,* but are almost always accompanied by hemorrhagic extravasation and necrosis, and frequently with cavity formation. The causative factors of this condition are mainly the same as those of suprarenal hemorrhage. Apart from infections and intoxications, chronic lung and heart disease, i. e., diseases tending to cause venous stasis, may produce inflammatory changes in the glands. It is believed that healing may occur, when the inflammatory process is of limited extent, with the formation of scar tissue. Primary suppurative processes within the suprarenals have been described in a few instances.

Lavenson attempted a classification of the various types of acute hypoadrenia, after an extensive study of case reports of this condition, collected from the literature. He was able to differentiate five clinical forms, on the basis of the preponderance of one or another group of symptoms: (1) Cases of sudden onset, with epigastric pain and tenderness, and marked abdominal symptoms (vomiting, meteorism, and diarrhea at times), followed by death within a few days—the so-called "pseudoperitonitic" type of acute suprarenal insufficiency; (2) The asthenic type, in which the essential feature is a profound asthenia, terminating within

* The term "adrenalitis," often used, should be discarded as a hybrid.

a few days in death, although in some instances the course may run for several months, a fact which led Bernard to describe a subacute form of suprarenal insufficiency; (3) The nervous type, in which the main symptoms may be either convulsions, delirium, or coma, or a typhoid state; (4) Cases of sudden death, in which at autopsy simply a destructive lesion of the glands, usually hemorrhage, has been found; (5) Cases associated with a purpuric eruption or hemorrhages into the abdominal viscera, occurring most commonly in children. This author has pointed out that although the majority of cases of acute suprarenal insufficiency may be classified in one or another of the foregoing groups, many cases are characterized by symptoms common to more than one group.

The occurrence of the syndrome of hypoadrenia, during the course of the various infectious diseases, has been repeatedly described in the literature of recent years. The clinical evidence of altered functioning of the various endocrin organs, resulting from infection, has been sought for by clinicians, and an endocrin factor has come to be regarded as a common cause of the modification of the clinical course of an infectious disease (Hutinel). In the opinion of Pende(*a*) and others, of all the endocrin glands the suprarenals are most commonly affected in the course of infections. It has long been known that these glands frequently show pathological alterations as a result of acute infections. Many writers have attributed to the organs a defensive function against the infectious process, but others, including Bernard, have not been able to find any evidence to substantiate this view.

This form of suprarenal failure constitutes the terminal hypoadrenia of Sajous's classification, or the subacute hypoadrenia of other writers. In some instances, the severity of the symptom complex, with fatal ending, conforms with the type of acute hypoadrenia. In the opinion of Sajous(*b*), this form of the malady results from the exhaustion of the secretory activity of the glands during the early stage of the infectious disease, such exhaustion being probably aggravated by temporary local lesions in the glands. The various clinical symptoms, which have been commonly attributed to this form of suprarenal insufficiency, are, asthenia, hypotension and hypothermia, cardiac weakness and feeble pulse, tachypnea, cyanosis; occasionally, anorexia, nausea, diarrhea, fainting spells, syncope or cardiac failure.

The syndrome has been observed, in different degree, in a great variety of infectious diseases, including diphtheria, typhoid and paratyphoid fever, influenza, pneumonia, bronchopneumonia, malaria, cerebrospinal meningitis, bubonic plague, malignant endocarditis, dysentery, epidemic icterus, scarlet fever, septicemia and tuberculosis. The lesions found in the glands at autopsy may be restricted to a reduction in the cholesterin bodies of the cortex, and a decreased chromaphil reaction, with possibly cellular atrophy and focal necroses, or in other instances, extensive in-

volvement of the glands, with cloudy swelling of the cortex, and complete absence of the lipoids, and hemorrhages of varying degree may be observed. In some instances the specific organisms have been obtained from the glands at autopsy. Paisseau and Lemaire have reported the finding of plasmodia in the suprarenals of patients dying from pernicious malaria. Some writers have maintained that the organs are especially vulnerable to certain infections, such as the toxin of diphtheria. An acute hypoadrenia has been so frequently observed in this disease that the designation "secondary syndrome of malignant diphtheria" has been applied to it (Morichau-Beauchardt). In the malignant forms of cerebrospinal meningitis an acute hemorrhagic epinephritis was so commonly encountered by Maclagan and Cooke as to suggest a selective action of the meningococcus on the chromaphil cells. These authors found a purpuric rash and a hemorrhagic condition of the suprarenals invariably present in such cases. In some instances the symptom-complex of the acute form of hypoadrenia may occur during the course of an infectious disease. Lowenthal has reported a case of this nature, following an attack of pleurisy and pneumonia, with symptoms of severe abdominal pain, constipation, and a slow pulse, in which at autopsy hemorrhages of both glands were found. Rashbrook and Carter observed the acute syndrome in association with tuberculosis. The patient had repeated attacks of epigastric pain, vomiting and constipation, with asthenia and hypothermia. Autopsy showed the suprarenals almost completely replaced by caseous masses. A similar case has recently been reported by Boyd, in which the glands were almost entirely destroyed by tuberculous lesions, no trace of medulla being left. One suprarenal showed the persistence of a small strip of cortex. The patient died in coma, a few hours after admission to the hospital, although until that time he had possessed sufficient vigor to engage in the full time duties of a military camp. The acute form has been described in bronchopneumonia by Sicard, in a case in which he noted extreme myasthenia, low blood pressure and marked hypothermia, and the presence of Sergent's "white line," and in which at autopsy the suprarenals were found to be hemorrhagic. Sajous(*b*) is inclined to regard the senile type of pneumonia, characterized by slight febrile disturbance, little or no cough, nor pain in the chest, and the rapid appearance of pulmonary edema, extreme asthenia, and hypotension, as not a true pneumonia, but as the clinical expression of a more or less sudden insufficiency of the suprarenals. The syndrome of hypoadrenia has been very commonly described in the course of typhoid fever. Some writers have, indeed, attempted to explain almost all of the symptoms occurring late in the course of the disease, such as hypothermia, hypotension, dicrotism of the pulse, hypocholesterinemia, and sphygmothermic dissociation, on the basis of suprarenal insufficiency. It is obvious that such broad conclusions are scarcely justified in the light of our present knowledge of the function of the glands.

The possible relation of the marked prostration following an attack of influenza to suprarenal insufficiency has been the subject of considerable discussion. Autopsy records appear to indicate that lesions in the glands are present in a large proportion of the fatal cases. Wolbach regards the minor acute lesions which are constantly found in the cortex in influenzal cases as not unlike those found in many infectious diseases, viz., the disappearance of the lipoid content and focal necroses. The more extensive lesions, such as hemorrhages, he attributes to secondary infection, usually with the *streptococcus hemolyticus*. In a special study of the pathology of epidemic influenza, Klotz observed changes in the suprarenal gland in 14 instances of 32 autopsies; these changes consisted of cloudy swelling of the cortex, occasionally small petechial hemorrhages, and the almost complete disappearance of the cholesterin bodies. This writer believes that there is evidence to show that in influenza the suprarenal gland does not function in a normal fashion, and that the storage of cholesterin esters does not take place. Cowie and Beaven have made a special investigation of the clinical evidence of the involvement of these glands in influenza and influenzal pneumonia, as a result of which they believe that the occurrence of suprarenal dysfunction is indicated by the presence of the cardinal symptoms of asthenia and hypotension, and by the characteristic rise of blood pressure following epinephrin injection; and further, that the prolonged blood sugar curve following the injection of epinephrin, and also following the ingestion of glucose is indicative of an endocrin disturbance in influenza.

The occurrence of an unusually severe form of hypoadrenia was commonly observed among soldiers, during the war, in the course of various infections, such as typhoid, malaria, epidemic icterus, and other infections. Pende(*b*) has offered an explanation of this severe type on the supposition of a pre-existing glandular exhaustion, due to excessive war fatigue (Sergent), and possibly in some instances to long-felt emotions (Cannon).

Several writers, in particular the French clinicians, have attributed the alarming symptoms (vomiting, headache, fever, profound depression, vertigo, and epigastric or lumbar pains) which sometimes follow antityphoid, and other preventive vaccinations, to a sudden suprarenal insufficiency (Sergent(*a*), Satre, and Loeper (*a*)). Other observers have attempted to explain, on a similar basis, the occasional occurrence of the so-called "nitroid crises" following the administration of arsphenamin (Beeson, Monziols and Collignon). No convincing evidence has been offered, however, in substantiation of this hypothesis.

The epinephrin content of the medulla, as well as the cholesterol content of the cortex, in various infectious diseases, has been investigated by a number of observers. In the majority of cases studied, a reduction in the epinephrin content has been demonstrated (Lucksch(*c*), Comes-

satti (*c*), Elliott and Tuckett), but in other instances a normal epinephrin index, or one slightly below normal, has been observed in certain infections, as typhoid, septicemia, and peritonitis (Sydenstricker). A marked reduction or disappearance of the cholesterin bodies appears to be a constant finding. The suggestion has been made that increased secretory activity of the suprarenals occurs during infections as a protective mechanism, and that a mobilization of the cholesterin bodies is related to the presence of the toxins in the circulation. Ragazzi, however, believes that the disappearance of epinephrin in infections is not the result of a chemical reaction between that substance and a toxin, but rather an indication of glandular insufficiency caused by bacterial lesions of the parenchyma.

The functional type of hypoadrenia has proved of special interest to endocrinologists. The term functional is employed to distinguish this form of glandular insufficiency from the other types in which, apart from any developmental defect or dysfunction which may be present, there is superimposed secondary organic alterations in the gland substance, in the form of destructive lesions. Sajous(*a*) has defined this type as the symptom complex of deficient activity of the suprarenal glands, due to inadequate development, exhaustion by fatigue, senile degeneration, or any factor that, without producing organic lesions in the organs or their nerve paths, is capable of reducing their secretory activity.

The symptom complex of functional hypoadrenia is less readily circumscribed than those of the acute and terminal forms. The clinical manifestations which have been ascribed by various writers to the functional type embrace a wide variety of somatic and psychic disturbances. The main symptoms include: asthenia, physical and mental; undue fatigability; cardiac insufficiency; feeble pulse; arterial hypotension; occasionally arrhythmia or bradycardia; vasomotor disturbances (sensitiveness to cold, cold extremities, occasionally "hyposphyxia" with venous stasis, or slight cyanosis of extremities); gastro-intestinal disturbances (dyspepsia, anorexia, vomiting, hyperchlorhydria, constipation); psychic disturbances (apathy, aboulia, faulty inhibition); drowsiness or insomnia; headaches; paresthesias; faulty metabolism. The symptoms in the individual case may be mild or relatively severe in character, and only a few of the group present. The duration of the syndrome is essentially chronic, but, if due to a temporary exhaustion of the gland, may be more or less transient.

It is now believed that many of the cases of functional hypoadrenia are due to a congenital inferiority of the chromaphil system. A high grade of defective development of the suprarenal glands is known to be frequently associated with a faulty growth of the brain (anencephaly and hemicephaly) and is incompatible with life. The suprarenal cortex develops early in the embryo, and is relatively large in the fetus. Chauffard found that as the gland increases in size in the fetus an increase in the cholesterol content takes place until at birth the average content is 15

gm. per kilogram. Verdozzi(*a*) observed that hypertrophy of the cortical tissue occurs during gestation, which he regards as substantiating the belief that the cortex is an important factor in the development and general nutrition of the organism. There is less positive evidence of the functional activity of the chromaphil tissue in the fetus. Lewis was unable to demonstrate epinephrin in human fetal suprarenals, noting in only two instances of full term glands inconclusive positive tests. Congenital inferiority of the chromaphil tissue is, however, believed to give rise to certain characteristic symptoms associated, in many instances, with *status hypoplasticus,* or *status thymicolymphaticus.* According to Wiesel(*e*) and Hedinger, hypoplasia of the chromaphil system is always present in *status lymphaticus.* It is known, also, that in advanced age the suprarenals lose their vascularity, diminish in size, and frequently undergo atrophy of a retrograde character. The glands, moreover, are regarded as especially vulnerable to the action of toxins, and it is believed by some that all the infections, general and focal, and intoxications, occurring during the life of the individual, may tend to impair the functional activity of these organs.

According to the reports in the literature the syndrome of functional hypoadrenia has been observed in many clinical conditions. The possible suprarenal origin of some forms of neurasthenia as indicated by the striking similarity in the symptom complexes of hypoadrenia and neurasthenia has been emphasized by Williams(*a*)(*b*) and others. It seems probable, however, that the epinephropathy is not the only factor in the causation of such neurasthenic symptoms, if, indeed, it plays any part, but that a dysfunction of other endocrin glands is associated with the suprarenal insufficiency, giving rise to the pluriglandular syndrome with uniglandular predominance of Pende. Many of the cases of neurasthenia, attributed to hypoadrenia might possibly be more properly classified under the thyrotesticular hypophyseal (suprarenal) syndrome of pluriglandular insufficiencies. In such cases there is usually an underlying constitutional inferiority, which predisposes to pluriglandular endocrinopathies in the presence of some noxa interfering with the function of constitutionally feeble glands (Wiesel).

In the opinion of many recent writers, functional hypoadrenia, due to fatigue or prolonged emotional disturbance, played an important rôle in the causation of the so-called war neuroses. Pende(*b*) believes that we may accept the hypothesis of a functional inhibition of the suprarenals due to war. Satre and Gros have described several types of cases, which they regard as fundamentally hypoadrenia, with asthenia, hypotension, gastric disturbances, and neurasthenic symptoms, resulting from the stress of war, acting upon the suprarenal glands, which although competent for civil life, are inadequate for the emergencies of active service. Carles has reported a number of similar cases, regarded as due to suprarenal

insufficiency, which are apparently of the same nature as the "shell shock" cases of the English writers. Sajous and Pende are inclined to attribute certain functional cardiopathies observed in soldiers to suprarenal exhaustion of neuropsychogenic origin. An adrenal form of asystole (asystolie surrénale) has been described by Josué, characterized by an enlarged heart with low arterial tension, and frequently complete arrhythmia and auricular fibrillation, with sudden death. At autopsy the suprarenals were found, in all of his four cases, to be extremely small or diseased, a fact which led this writer to presume that the heart was suffering from lack of physiologic stimulus supplied normally by the suprarenals.

Other writers have attributed certain forms of gastropathies to hypoadrenia. Loeper has described a suprarenal dyspepsia (dyspepsie surrénale) manifested by atonicity and constipation, while Hernando has stated, as a result of his research, that suprarenal insufficiency appears to induce conditions favorable for the development of gastric ulcer. He observed gastric ulcers in some cases of severe hypoadrenia. Suprarenal insufficiency has been the alleged causative factor in many other clinical disorders, such as manic-depressive psychosis (Rossi), and seasickness (Naamé).

In many instances of reports in the literature concerning the occurrence of hypoadrenia in various disorders, the hypothesis of a suprarenal origin of the syndrome has been assumed on the observation of the beneficial results following the administration of suprarenal gland extract or epinephrin. Clinicians have at times fallen into the error of identifying the pharmacological action of the extract of the gland with the physiological function of the suprarenal. There is, as a matter of fact, little or no clinical or expermiental evidence to warrant such assumption, and much evidence distinctly controverts it.

As has already been emphasized, the making of a positive diagnosis of any form of hypoadrenia *intra vitam* is a difficult matter. It seems possible, however, that in the more outspoken types of acute hypoadrenia, associated with suprarenal hemorrhage, or acute epinephritis, a diagnosis might justifiably be made. The abrupt onset of the condition, the lumbar or epigastric pain, the rapid fall in arterial pressure, the severe gastrointestinal disorders (vomiting, diarrhea), and the grave collapse, should arouse the suspicion of the physician as to the sudden failure of suprarenal function. The clinical condition may be confused with that of acute hemorrhagic pancreatitis. According to Lavenson's observation, the shock is more profound, the lumbar tenderness more acute, and the epigastric pain and vomiting less marked in acute hypoadrenia than is the case in acute hemorrhagic pancreatitis. Acute hypoadrenia is also to be differentiated from various acute poisonings. It has been mistaken in some instances for peritonitis, appendicitis, cholera morbus, and cerebral apoplexy.

In the course of the infectious diseases, with a sudden lowering of the blood-pressure, and a fall in the temperature, marked prostration, chilliness and possibly anorexia, nausea, or diarrhea, the probability of suprarenal involvement should be kept in mind. The "white line" of Sergent may be present in such cases and offer an aid in diagnosis, although this phenomenon is by no means pathognomonic of suprarenal insufficiency.

In suspected cases of functional hypoadrenia, the study of the general constitution for evidence of congenital inferiority in the chromaphil system* and other endocrin glands, and particularly a search for signs of *status thymicolymphaticus* may assist in arriving at a conclusion.

There is no specific therapy for hypoadrenia. The use of epinephrin, and of the gland extract, has been recommended by many clinicians, some of whom have reported encouraging results, in various forms of hypoadrenia. In the acute type, with destructive lesions in the glands, such therapy offers little hope of ameliorating the symptoms. Sajous(*a*) has recommended the administration of physiological saline solution, intravenously, in the emergency cases of suprarenal hemorrhage, along with the use of such drugs as amyl nitrite or nitroglycerin. In the form of hypoadrenia, supervening in the course of acute infectious diseases, several observers have reported beneficial results from the hypodermic administration of epinephrin (15 minims of a 1:1000 solution). Sammartin has recommended the oral administration of epinephrin, 5 minims or more, every three hours, to keep the blood pressure normal in typhoid fever, reporting good results in six cases thus treated. The intratracheal administration of epinephrin, by means of a spray, has been advised by Wolff-Eisner, in the treatment of influenza and influenzal pneumonia. Inasmuch as the effects of epinephrin are transient, Sajous advises small repeated doses (10 minims every two or four hours), given hypodermically, during the stage of assumed suprarenal failure in the acute infections. The intraspinal administration of epinephrin (3 c.c.) has been suggested by Auer and Meltzer(*b*), these authors having observed a more prolonged elevation of the blood pressure following this method of administration. In the so-called "nitroid crises" following the administration of arsphenamin, as well as in the anaphylactic phenomena associated with bacterial inoculations, some writers have found the administration of epinephrin of great therapeutic value, attributing such phenomena to a sudden arrest of suprarenal function. The prophylactic administration of epinephrin, some hours before the making of an antityphoid inoculation, has been advised by Satre, Loeper(*a*) and others. Some observers have, however, failed to confirm such beneficial results from the use of epinephrin in these conditions. Cowie and Beaven found that it was of no aid in the treatment of influ-

* In this connection it should be borne in mind that animals survive perfectly well what appears to be complete suppression of epinephrin discharge from the suprarenals. R. G. H.

enzal cases. Wagner believes that the use of epinephrin in influenza is indicated only when the condition is complicated with pneumonia, and the lungs are rapidly invaded by a serous exudate. Jaksch-Wastenhorst states that no benefit is to be derived from the use of epinephrin in pneumonia and warns against its use. The future must reveal the true value of such therapy in the hypoadrenia of acute infections.

In the treatment of the purely functional forms of hypoadrenia, the glandular extract has usually been employed. The use of epinephrin, over prolonged periods, in this condition is clearly contra-indicated. Some encouraging results have been described, especially in those forms of neurasthenia in which suprarenal deficiency has been regarded as a causative factor. Some observers have preferred a pluriglandular form of therapy, since the other endocrin glands are usually involved in this condition, and have, in many cases, administered several gland products, quite empirically, without due consideration or knowledge of the functional interrelation of the glands involved. Our knowledge of organotherapy is as yet too limited to justify such indiscriminate endocrin polypharmacy. To feed the body with hormones some of which are potent and toxic, and allow the organism to select the deficient hormone, would appear to be pseudo-science.

Conclusion

In conclusion it may be emphasized that most of the literature on "hypoadrenia" betrays a profound ignorance (of modern suprarenal physiology) upon the part of the writers and a remarkably cavalier attitude toward the canons of logic. It is probably safe to forecast that, a decade hence, much less will be heard of clinical suprarenal deficiency.

Pseudohermaphrodism . . . . . *Wm. C. Quinby*

Classification—Clinical Cases.

Clinical Syndromes due to Suprarenal Diseases

Pseudohermaphrodism

WM. C. QUINBY

BOSTON

English—*Pseudohermaphrodism.* **French**—*Erreur de sexe.* **German**—*Zwitterbildung.*

The term pseudohermaphrodism signifies an anomaly of either the external or internal genitalia, which, combined with the bodily habitus—the so-called secondary sexual characteristics of Hunter,—creates a condition in which the true sex of the individual may at first glance be uncertain.

Such instances of doubtful sex have been noted from the earliest recorded history of the human race and have always gained marked attention. In the earliest forms of man's conception of the deity both the Indic religion and Egyptian writings frequently include a dual sex. This godly attribute has been preserved in Greek mythological lore in the history of the adventure of the son of Hermes and Aphrodite, Hermaphroditus, at the pool of Salamacis, from which story our present term for the condition of dual sex originates. Since, however, more recent knowledge has shown that the power of self-fertilization and procreation is not possible for organisms of the class of vertebrates, the prefix *pseudo* has been added to the word hermaphrodite.

The final decision as to the sex of an individual must rest upon the characteristics, gross or microscopic, of the gonad. But frequently such an examination cannot be made, at least during life. The usual judgment as to sex, therefore, is made from those bodily characteristics which occur at the time of puberty and which differentiate the previously infantile type of body into either the male or female type. As male characteristics we find at this time the change in voice due to the growth of the larynx, and the growth of the beard. In girls the breasts enlarge, fat is deposited over the thighs, the pelvis expands and menstruation appears. Whenever changes characteristic of secondary sexual habitus occur in the presence of the opposite sex gland then a condition of mixed or doubtful *sexe ensemble* is produced.

Under such circumstances anomalies are also usually found in the

genital system, both internal and external. These may rarely involve the sex gland itself causing the occurrence of the so-called ovo-testis, an organ

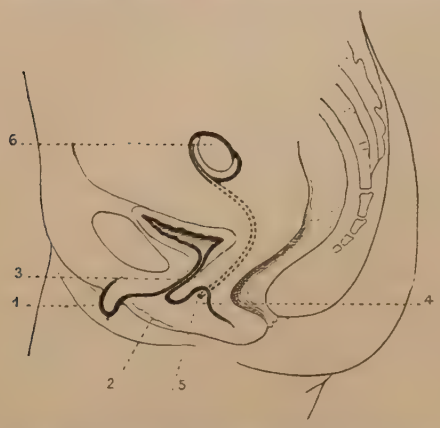

Fig. 1. Masculine hermaphrodite of the external type with separation of the urogenital canal. 1. Phallus. 2. Urogenital sulcus. 3. Urethra. 4. Vagina. 5. Opening of the ejaculatory duct. 6. Testicle. (From Tuffier et Lapointe.)

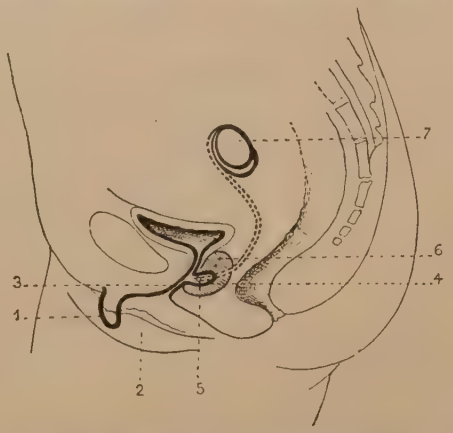

Fig. 2. Masculine hermaphrodite of the external type with persistence of the urogenital canal. 1. Phallus. 2. Urogenital sulcus. 3. Urogenital canal. 4. Rudimentary male vagina. 5. Ejaculatory duct. 6. Prostate. 7. Testicle. (From Tuffier et Lapointe.)

in which the histological components of both testicle and ovary are to be found. Such organs have not been demonstrated to be fertile either as

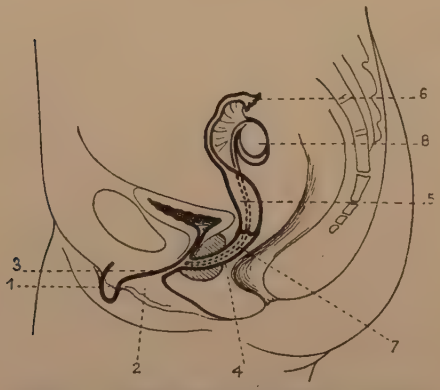

Fig. 3. Masculine hermaphrodite of the complete type with persistence of the urogenital canal. 1. Phallus. 2. Urogenital sulcus. 3. Urethra. 4, 5, and 6, Vagina, uterus, and tube. 7. Vas deferens. 8. Testicle. (From Tuffier et Lapointe.)

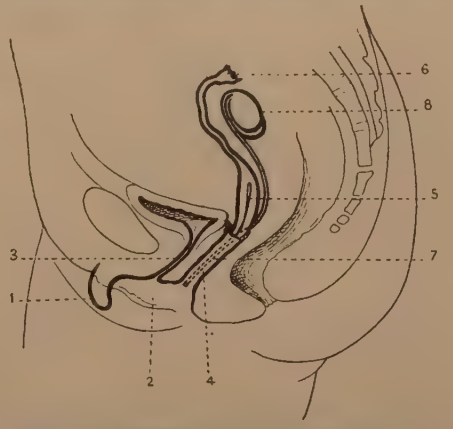

Fig. 4. Masculine hermaphrodite of the complete type with separation of the urogenital canal into the urethra and vagina. 1. Phallus. 2. Urogenital sulcus. 3. Urogenital canal. 4, 5, and 6, Vagina, uterus, and tube. 7. Vas deferens. 8. Testicle. (From Tuffier et Lapointe.)

an ovary or as a testicle, and though Pick(*a*) has reported their occurrence in swine, they are very rare in man.

The commonest anomaly involves the tubular portions of the genital system. The normal persistence of either the Müllerian or Wolffian ducts

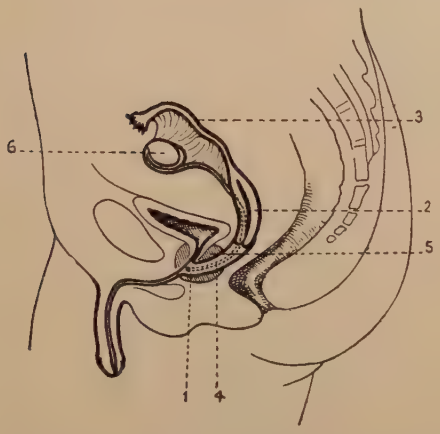

Fig. 5. Masculine hermaphrodite of the internal type. 1. Vagina. 2. Uterus. 3. Tube. 4. Vas deferens. 5. Prostate. 6. Testicle. (From Tuffier et Lapointe.)

Fig. 6. Female hermaphrodite of the external type. (Hypertrophy of the clitoris.) (From Tuffier et Lapointe.)

with their appendages and the descent of the testis or ovary is described and illustrated at length in all works on embryology and will not be re-

Fig. 7. Female hermaphrodite of the external type. (Hypertrophy of the clitoris and persistence of the urogenital canal.) 1. Persisting urogenital canal. 2. Prostate. (From Tuffier et Lapointe.)

Fig. 8. Female hermaphrodite of the external type with fusion of the labia majora. 1. Urethra within the clitoris. 2. Persisting urogenital canal. (From Tuffier et Lapointe.)

peated here. The Müllerian system forms the female internal genitalia, the Wolffian the male.

The partial persistence of portions of one system in the presence of the other produces the anomalous conditions usually seen. The varieties of forms of maldevelopment which can occur are best seen in the schematic illustrations of Tuffier and Lapointe.

From the above considerations it is easily seen that there is opportunity for much variety in the types of pseudohermaphrodism which can occur, for the irregularity may involve the sex gland itself, or the external genitalia or the internal gentalia, and all may be accompanied by confusing secondary sexual characteristics. Several writers have constructed classifications showing such possible combinations. That of Pick(*b*) adapted from Poll is the most comprehensive. This writer considers all attributes of sex to be either (a) *essential* or *germina*, or (b) *somatic* or *accidental*. The first are inherent in the opposed differences of the embryological cells and are therefore differences due to the gamete. They determine exclusively the sex of the individual, whether male or female. The second group of attributes are numerous and are divided into (1) those *characteristics subsidiary to the genitalia* either internal or external and (2) those not so related, or *extragenital*. To the first group belong the genital ducts and their accessory glands, together with the penis, scrotum and vulva, while to the second belong the larynx, pelvis, and psychic make-up; together with the hair distribution, pigmentation of skin and, in fowls, the feathering.

Considering hermaphrodism in general as a mixture of opposed characteristics there are various possibilities in the above scheme. An individual may be mixed in the germinal attributes only or in the somatic only or there may be a mixture of each. If only the somatic attributes are mixed we have the commonest condition found in which an individual of definite sex shows characteristics *apparently* of the opposite one to a greater or less degree.

Clinical Cases.—From the literature Neugebauer has collected the reports of over 2000 cases of pseudohermaphrodism showing every variety of type. It will suffice here to report two cases observed by the writer as illustrative of these anomalies.

Case 1. Male pseudohermaphrodite showing female secondary sexual characteristics.

Rae Marion R., No. 10432, an unmarried negress seventeen years of age, entered the Peter Bent Brigham Hospital on the seventh of May, 1919, complaining of pain in the lower abdomen and a tender mass in the right groin. Both father and mother are living and well, as are also two sisters and one brother. There was no history of tuberculosis or insanity in the family. The patient's general health has always been good. She was born in Virginia, but since infancy has lived in Massachusetts. The only disease of childhood of which there is a history is measles. At the age of six the patient was operated on for bilateral hernia. Patient has been through eight grades of grammar school, following which she

went to a trade school where she learned dressmaking. Memory and disposition have been normal. She has never had any menstrual period, nor any sensation suggestive of such. Her mother states that this condition is also present in the patient's maternal aunt. Three years ago the patient weighed 150 pounds. She now weighs but 105 pounds.

Present illness: Three months ago the patient began to have intermittent pain in her back and on the left side of the abdomen. This gradually has become more severe so that for the past two weeks it has been con-

Fig. 9. Case I. Male pseudohermaphrodite. Note that the skeleton shows none of the characteristics of the female. The breasts and external genitalia, however, are of the female type. (Original.)

Fig. 10. Case I. From the rear. (Original.)

tinuous. During the last two weeks the left side has become very tender to pressure so that she has been unable to tolerate a corset. During this same period the patient felt very weak and has not been able to help with the usual household duties at home. There have been no urinary symptoms. Appetite has been very poor. There has been some slight fever, but no chills. There has been a slight cough during the last three months.

Physical examination shows a colored girl who evidently has lost considerable weight. The general outline of the skeleton shows it to be of the infantile or undifferentiated type. There is no axillary hair and prac-

tically no pubic hair. The breasts are of normal adolescent female type. Examination of the lungs shows moderately active tuberculosis. In the abdomen there is marked spasm and rigidity in the left quadrant varying in tenderness. In the right groin is a mass about 4 x 2 cm. which appears to be forcing its way into the region of the labium majus. This mass is slightly tender on palpation. Vaginal examination shows normal external genitalia of the female. The introitus admits two fingers, and there is no evidence of a hymen. The vagina is short, possibly one-half the normal length, and ends blindly, no vestige of cervix or uterus being demonstrable either to sight or touch. Rectal examination was negative. Temperature was 104° in the evening, normal in the morning; pulse 70–90; respirations 20–25; the white blood count averaged 17000; hemoglobin was 70 per cent.

The table of bodily measurements follows:

Weight	47	kg.
Height—standing	177	cm.
Height—sitting	90	
Span of arms	182	
Girth of chest at rest	76	
" " " on inspiration	79	
" " " " expiration	73	
Length of head	25	
Width of head	15	
Height of face	17.5	
Width of face	14	
Height of palate to incisor teeth	4.5	
Circumference of neck below the thyroid cartilage	29	
" " abdomen at umbilicus	66	
Distance between anterior superior spines	27	
" " iliac crests	34	
" " femoral tuberosities	32.5	
" " umbilicus and sternal notch	36	
" " acromion processes	37	
" " ant. sup. spine & patella (rt.)	52	
" " " " " " " (lft.)	53	
" " " " " " int. malleo. (rt.)	93	
" " " " " " " " (lft.)	93.5	
Length of feet (each)	28	
Circumference of thigh (each)	38	
" " knee (each)	37	
" " calf (each)	26	
Distance between acromion and olecranon (each)	38	
" " olecranon and ulnar styloid (each)	30	

Circumference of biceps (rt.)	19	cm.
" " " (lft.)	18.5	
" " forearm (rt.)	19.5	
" " " (lft.)	19	
" " wrists (each)	14	
" " hands (each)	19.5	

On the tenth of May, 1919, the mass in the lower left portion of the abdomen was investigated by operation and was found to be omentum matted together by tuberculosis. Throughout the abdomen, also, there were extensive areas of miliary tubercle together with much granulation tissue which bled easily on touch. There was practically no ascites present. Investigation of the pelvis showed an entire absence of internal genitalia of the female type. Palpation of the region at the neck of the bladder failed to find any structure suggestive of a prostate. The small mass in the right groin was removed and found to be a rudimentary undescended testicle which also showed evidence of tuberculosis. The patient died at home of tuberculous peritonitis on the twelfth of July, 1919. No autopsy was obtained.

The pathological report, made by Dr. S. B. Wolbach, of the mass found in the groin is as follows:

Tenth May, 1919. Material: Orchid.

Gross description: Specimen consists of a piece of tissue about 7 x 2½ cm., about two-thirds of which consists of an oval shaped portion which on section contains a typical light brown spongy tissue of a testicle with, however, numerous strands of fibrous tissue which give it a very tough and fibrous consistency. There are numerous miliary, yellowish, opaque areas scattered throughout this portion of the tissue. Surrounding this mass is a fibrous capsule about 2 mm. thick. Covering a greater part of the entire mass is a thin layer of tuberculous granulation tissue in which are numerous pale tuberculous appearing nodules from 1-3 mm. in width. Tissue is fixed in Zenker.

Microscopic report: There are four sections of the tissue which show it to be a rudimentary orchid with atypical spermatogenesis. The parenchymatous portion consists of alveolar structures of columnar or polyhedral cells inside a basement membrane, with, usually, a narrow central lumen in which are many hyperchromatic dot-like bodies. These, however, cannot be identified as mature spermatozoa, although they probably represent some stage in the spermatogenetic cycle, though possibly only pyknotic nuclear remains.

Many of these alveolar structures seem to be well defined seminiferous tubules with atypical spermatocytes in layers two and three cells deep, and a few more or less spindle shaped cells with small, pale nucleus, probably Sertoli cells. No karyokinetic figures are seen. Many tubules

show regressive changes, especially those of keratinization and hyalinization.

The organ is irregularly divided into lobules by thick bands of fibrous tissue. Surrounding the tubular portion is a thick layer of fibrous tissue upon which is superimposed in places tuberculous granulation tissue.

Diagnosis: Rudimentary orchid, with atypical spermatogenesis and tuberculous periorchitis.

It is evident from the histological picture of the gonad that we are here dealing with a case of male pseudohermaphrodism showing secondary sexual characteristics of the female together with female external genitalia. The possibility that such conditions of hermaphrodism may have a familial aspect is suggested in the permanent amenorrhea of this patient's aunt. A few other instances occur in the literature illustrative of this occasional tendency.

Fig. 11. Histological picture of the gonad in Case I, showing type of testicle characteristically found in cryptorchids.

A second case of the opposite type is well illustrated by the following which has already been reported by me in 1916.

Case 2. Female pseudohermaphrodite showing male secondary sexual characteristics.

Robert S. was admitted to the Brady Clinic of the Johns Hopkins Hospital on June 8, 1915, for hypospadias and undescended testicles. He was ten years old in July, 1915.

The family history relates that one brother died at birth, and one at seven months of age. One younger sister is living and is normal. Both parents are well; they are first cousins. The father has a slight hypospadias with the meatus about half an inch below the apex of the glans.

Until two years of age the patient suffered from "marasmus," but otherwise has been entirely well and strong, and has had none of the exanthemata. His mentality is considered good, and he is now in the third grade, although attendance at school began only two years ago. His habits and activities are those of a normal boy: he spurns girlish pursuits, and much prefers such games as football. The pubic and axillary hair has been present for four years. The voice has always been "coarse" and the hands and feet "stubby." Since birth the urethra has opened at the

base of the penis and the testes have not descended. There is an entire absence of any history of abdominal pain or crises suggestive of retained menses, and there has never been any bleeding from the penis. Libido has not appeared as yet.

Physical examination finds the general bodily condition and color excellent. The musculature is well developed. The head is rather large,

Fig. 12. Case II. Female pseudohermaphrodite. Front view of body. (From the Johns Hopkins Hospital Bulletin, February, 1916.)

Fig. 13. Case II. Lateral view, with the patient standing, to show the general pose and round shoulders. (From the Johns Hopkins Hospital Bulletin, February, 1916.)

with prominent frontal regions, and the shoulders, though broad, are markedly stooping. The forehead is of moderate height; the face is broad; the lips are thick; the nose is flat. The hair, dark brown in color, is rather coarse, and is lacking over each lateral frontal region. The eyebrows are more sparse in their outer portions than toward the root of the nose. The eyes, ears, and mouth are normal. The ears show no stigmata and the upper central incisors are no broader than the other incisor teeth.

The palate is moderately high. There is a considerable amount of fine hair on the upper lip; the axillary and pubic hair is abundant, the latter showing the female type of distribution. The hands are broad and short; the finger-nails have been bitten. The skin over the body is somewhat harsh. There are no abnormal deposits of fat. On examination, the heart, lungs, and abdomen are entirely normal. The breasts are undeveloped and

Fig. 14. Case II. The external genitalia. Note the phallus with prepuce, and labia majora simulating a bifid scrotum; also the extensive growth of hair and the coarse skin. (From the Johns Hopkins Hospital Bulletin, February, 1916.)

of the male type. Very careful palpation shows no signs of any abdominal mass. There is no unnatural pigmentation of the skin. The growth of hair below the knee on each leg is in marked excess.

On examination of the genitalia, the phallus is found to be represented by an organ 5 cm. long, curved markedly toward its ventral surface. There is a well-developed prepuce drawn into folds on the dorsum, but not uniting completely in the midline on the ventral side. This covers the glans, which is well developed except for the meatus, which is replaced by a ventral grove. At the base of this structure, between it and the slightly

prominent mons, the skin rises in a fold, and encircling the phallus, extends downward on either side to form the bifid scrotum or labia majora. No testes or spermatic cords are to be felt anywhere. When the glans is drawn upward, the opening of the urethra is seen at a point corresponding to the peno-scrotal junction. From this to the tip of the glans the middle line shows a longitudinal gutter covered by striæ of mucosa.

Fig. 15. Case II. The external genitalia with the labia separated and the phallus raised. The median furrow of mucosa is seen, bearing the urethral opening, represented by a dark spot half-way between the examining fingers and thumbs. Note the entire absence of vagina. (From the Johns Hopkins Hospital Bulletin, February, 1916.)

The perineum from meatus to anus is smooth and without trace of depression. There is nothing to suggest labia minora. An abundance of hair is present, and the skin of the perineal region and adjacent thighs is harsh and coarse.

There is a definite lack of equilibrium on the part of the superficial vasomotor system. The hands are cold, clammy, and often of dusky hue; the skin of the body shows mottling on cooling, and the patient blushes very readily. All the other reflexes are lively, but there is no cremasteric reflex.

Rectal examination shows an apparent absence of the prostate, al-

though in the region above this area there is felt a small mass which is about 2 cm. long and 1 cm. broad, not tender, and only slightly movable.

Radiographs of the head, chest, abdomen, pelvis and hands are entirely normal. The urine is normal, and the ingestion of 150 grams of dextrose caused no glycosuria. The phenolsulphonephthalein output was 60 per cent during the first hour. The Wassermann test was negative. Blood-pressure: Systolic, 115; diastolic, 90. Blood count: Red blood cells, 5,128,000; white blood cells, 7,780.

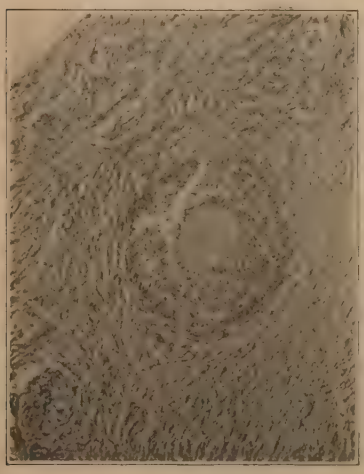

Fig. 16. Low power magnification of gonad in Case II showing Graafian follicles containing ova in various stages of development. (From the Johns Hopkins Hospital Bulletin, February, 1916.)

An operation was performed on June 14, 1915, to better the hypospadic condition and to search for the supposed testicles and bring them down. No trace of the spermatic cord could be found in the inguinal canal. On entering the abdomen I discovered an infantile uterus with tubes and ovaries of normal appearance. An ovary, with adjoining portion of its tube, was excised for histological examination.

The specimen consists of an ovary 2.5 x 1.3 x 1.7 cm., together with about 5 cm. of tube, bearing normal fimbriæ. Running from one side of the ovary is a layer of very thin tissue, apparently a bit of the broad ligament, containing on one surface a small, very flabby mass in the position of the parovarium. The surface of the ovary is smooth, and one section is seen to contain numerous areas varying in size, presumably follicles. The larger of these contain bloody fluid, the smaller watery fluid.

Microscopic Examination: Sections of the ovary show a typically normal structure. Graafian follicles contain ova in various stages of development. No corpora lutea are seen, although there is in one area a splendidly preserved corpus fibrosum. A careful search failed to show any abnormal elements.

The Fallopian tube shows the usual papillary-like foldings of mucosa with normal epithelium.

The parovarium shows numerous tubules, thin-walled, and having a single layer of epithelium.

It is evident from the foregoing that we are dealing here with a case of atypical sexe-ensemble. The sex of an individual must always be determined by the nature of the gonad, regardless of the presence of abnormalities either of other parts of the genital system or of the secondary sexual manifestations of the body as a whole. Consequently, this pa-

tient is of the female sex; and this in spite of so many secondary characteristics of the opposite, male, sex.

In the sphere of the internal genitalia the development has followed a normal course; uterus and ovaries are present, and are normal so far as examined. The external genitalia, however, show many deviations from the normal female type. The urethra opens in its usual position, but the clitoris is much overdeveloped, closely resembling a penis of the hypospadic sort, and there is no external trace of vagina. It is to be presumed, on morphological grounds, that a rudimentary vagina exists, but attempts to examine the posterior urethra with an endoscope were without conclusive result because of the small size of the structures.

The patient, therefore, belongs to the class of female pseudohermaphrodites of the external type. But though the external genitalia are atypical, it is in the domain of the secondary sex characteristics that the most marked deviations are found. The voice, the hair on the face, the general bodily habitus, and the mental processes are all of the heterologous male type. Indeed, on adding the precocious hair development to the above appearances, this individual seems to possess a degree of maleness considerably greater than that usual in normal children at ten years of age. Only the distribution of the pubic hair and the configuration of the thighs remain of the female type. In this respect the case is unusual, for though over two thousand case reports of pseudohermaphrodites are to be found in the literature, those bearing the male gonad are about ten times as common as those bearing the female; and in these latter only a few reports describe such complete presence of the heterologous secondary manifestations of sex.

Of late years attempts have been made to produce hermaphrodites artificially in mammals by transplantation of the sex gland. Steinach (*a*) to (*f*) inclusive, especially, has apparently obtained remarkable results in cases where a sex gland of one sex was transplanted into a young castrated animal of the opposite sex. There followed a masculinization of the female host or a feminization of the male one. Further, he found the gonad of one sex to have definite inhibitory powers on the growth of a transplant of the opposite one. This was supposed to represent a hormone antagonism. These observations were made on guinea pigs and rats. Recent work by Moore has been successful, however, in proving that castration of the host is not necessary, and that a sex gland can be successfully transplanted to an animal of the opposite sex which retains one normal gonad.

Other evidence of possible gonadal hormone antagonism has been brought forth by Lillie(*a*)(*b*) in his investigations concerning the occurrence of the "free-martin" in cattle. He found that in such cases the twin fetal circulations were connected through an anastomosis of the blood vessels of the allantois. Under these circumstances when the twins were male and female the ovarian development was suppressed in the female

of the pair. He offered as an explanation of this condition the assumption of a dominance of the male gonadal internal secretion over that of the female.

On the whole, however, enough evidence already exists to prove conclusively that there is a definite internal secretory activity (hormone production) in both the ovary and the testis, and that although the interrelation of these hormones, whether antagonistic or not, is as yet not clearly understood, a dysfunction of the internal secretory properties of the gonad is doubtless the cause of the appearance of such conditions as are found in the pseudohermaphrodite.

Pubertas Precox ..... *Henry D. Jump*

Synonyms—Thymus—Pituitary Gland—Anterior Portion—Suprarenal Gland —Gonads—Summary.

Clinical Syndromes due to Suprarenal Diseases

Pubertas Precox

HENRY D. JUMP

PHILADELPHIA

Synonyms: (Macro genito somia precox, Precocious Puberty, and Precocious Maturity.)

Pubertas precox may be defined as that condition in which the secondary characteristics of sex appear before the usual age of puberty, with manifestations of sexual maturity. The subjects show rapid growth of body weight and height often; increase in size of penis and testicles in boys, of the labia and breasts in girls: growth of hair on the pubes, in the axillæ and also, in the case of boys, on the face: greater prominence of the mons veneris. The girls menstruate more or less regularly: J. L. Morse in 1897 referred to cases which became pregnant respectively at 8, 8½ years and 11 years. Beekman says sexual desires appear tardily, but of the 151 cases which he collected 11 became pregnant. The boys show frequent erections, pollutions and masturbation. Modesty is usually no more developed than in children of the same age except at the menstrual period, when bashfulness may also be manifested. The mentality of these children is usually that of others of like age. In some, however, it is precocious as in the case of Frankl-Hochwart, a boy who asked questions concerning immortality. On the other hand in some the mentality is low. In a few the child appears otherwise to be in normal health. Von Haller quoted by Falta(*d*), reports a girl who began to menstruate at 2 years of age, became pregnant at 8 and lived to be 75 years old. Many however who have tumors of the brain exhibit other signs of brain tumor and die fairly young.

The condition must not be confused with the irregular genital bleeding often seen in new born female infants, which lasts a short time and does not recur. It must be differentiated from Virilismus, in which precocious bodily and mental development are associated with unusual growth of hair on the mons and face and in the axillary regions; in this condition menstruation and other signs of sexual maturity do not occur.

Evidence is cumulative that development of secondary sexual characteristics is dependent upon influences emanating from certain endocrin-

ous glands. We refer to the thymus, anterior pituitary body, pineal body, suprarenal body and the gonads. They may act as accelerators or inhibitors.

If one be acceleratory we should look for a hyperplasia and increase of function in it at the time of puberty: stimulation of it as by a certain class of tumors should cause precocity: ablation should delay development; feeding or transplantation of the gland from young animals should cause precocity.

If one be inhibitory we should find it atrophying at puberty: a destructive tumor in it or ablation of it should hasten puberty; feeding of the gland should delay puberty.

In none of the glands are all of these conditions fulfilled. In some a part are, in others the testimony is conflicting. From the evidence available we are warranted in believing that all of these mentioned have an influence upon the development of these characteristics and of believing that there is probably a relation or correlation of function in them all.

Alterations therefore in the functions of the glands governing the normal development of puberty should be looked for in cases of abnormal development. Such alterations have been found in reported cases in the pineal body, anterior pituitary body, suprarenals, and gonads.

The evidence has been clinical, associated with the pathological findings in those cases of precocity which came to autopsy, and experimental: ablation of glands and feeding to young animals the raw glands or the desiccated preparation of them, taken from young animals. It is unfortunate that, in some of the cases in which autopsies were done, the associated ductless glands were not examined.

Thymus

This gland shows signs of involution at the time of puberty. According to Waldeyer and Hammar it grows up to the age of puberty and then loses weight but continues to functionate in less intensity even into old age. Calzolari found that in castrated male rabbits the thymus atrophies more slowly than normally. Normal involution would seem to depend on the development of the sexual organs. Marine and Manley experimentally removed the thymus from young animals and saw a hastening of sexual maturity in them. On the other hand E. A. Park could detect no changes in the procreative functions of thymectomized guinea pigs. Hewer fed thymus to young male white rats and found a delay in the development of the testes. When the gland was fed to adult rats a degeneration of the testes followed. There are no reports on the condition of the thymus in cases of precocious puberty. It would seem, however, that we are justified in believing that this gland has an inhibiting effect upon sexual development.

Pineal Body or Epiphysis

It is believed that this body begins to atrophy at the 7th year, but that portions of it are still active in adult life. Cases of sexual precocity associated with tumor of the pineal have been described by Frankl-Hochwart, Ogle, Oesterreich-Slavyk and Horrax. Frankl-Hochwart's case was a boy of 5½ years who was as large as one 9 years old. His testicles and penis were as large as of one 15: his mentality was developed far beyond his years. The autopsy showed a teratoma of the epiphysis. Ogle's case was a boy of 6 who had a penis like that of a boy of 16-17. The testicles were not enlarged: masturbation was practiced: pubic hair was plentiful. A teratoma of the pineal was found in this case also. It is of interest that *all of these cases were boys* and that in none of them was reference made to growth of hair on the face. These reports have led to the experimental removal of the epiphysis in young animals.

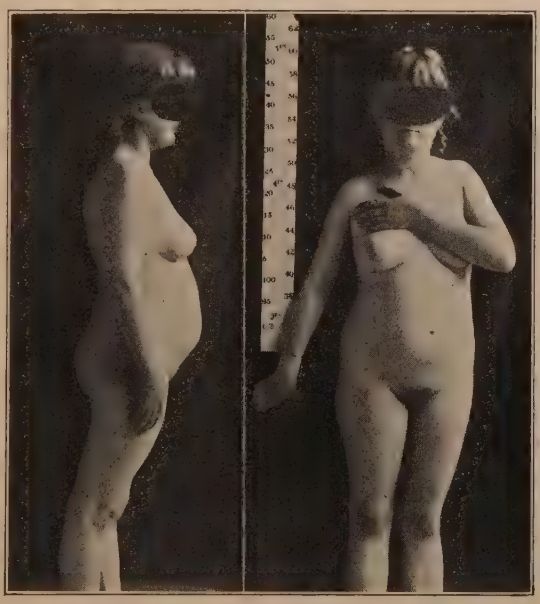

Fig. 1. Case of Dr. Gilbert Horrax. Reproduced by author's permission from Arch. Int. Med. 1916. XVII. 629. Girl of 11 years, height 152 cm. (60 in.), (114 lbs.). At one year began to develop abnormally physically; menstruated regularly and showed other secondary characteristics just before 11 years. Supposed to be a case of pineal disease; X-Ray showed enlargement of sella turcica.

Horrax successfully removed it in guinea pigs and rats. The male guinea pigs showed a hastened development of the sexual organs. There was, as compared with the controls, a relative increase in the size and weight of testes and seminal vesicles: these organs also showed, histologically, a more advanced stage. In the females there was no demonstrable change in the genitalia, but they seemed to show a tendency to breed earlier. In the rats there was some evidence of hastened maturity but the observation could not be completed. Foa(*a*) removed the pineal from young chickens and noted that the males showed a greatly accelerated sexual development: the females showed no effect. In the puppies and guinea pigs experimented upon by Sarteschi(*b*) there was an increase in the size and weight of the testes.

It is noteworthy that in these ablation experiments results were seen *in males only*, just as in tumor of the pineal body, sexual precocity was seen in boys only.

On the other hand the experiments done by Dandy on puppies and rabbits with extraordinarily careful technique showed no results. This was confirmatory of the work done previously by Biedl(*d*), and Exner and Boese.

Feeding experiments with fresh or dried pineal have been conducted on young animals by Dana and Berkley, and McCord(*a*). The former noted that the subjects outgrew the controls in activity, size, intelligence and resistance to disease. McCord found that chicks, puppies and guinea pigs showed increased growth and the guinea pigs bore young earlier. This is the same condition as is seen in children suffering from pineal tumor, and in animals subjected to pinealectomy.

We have then here *a conflict in evidence* offered which is hard to reconcile; one seeming to indicate that the organ is inhibitory and the other that it is acceleratory to sexual development.

The pineal is so situated that it is difficult to operate upon. Many of the experimental animals die from hemorrhage or other causes. There are so many other important structures contiguous to this organ that it seems impossible that some are not injured by the traumatism incidental to extirpation or on account of the exudate which may follow it. Hydrocephalus develops with tumors of this region and may affect, by pressure, the function of the pituitary gland. The possibility of such neighborhood effects must be taken into consideration in the attempt to explain the sexual changes which occur. In this connection McCord argues that the precocity seen in tumor cases may be due either to a disturbance of the endocrinous balance which governs the pineal secretion or the tumor cells may retain the functional characteristics of normal pineal cells and thus increased secretion may follow.

Pituitary Gland

Anterior Portion.—A relationship exists between the pituitary gland and the gonads. This has been shown by the facts that during pregnancy there is hyperplasia of the gland (Erdheim and Stumme) and that in castrated animals there is a hyperplasia as has been shown by Tandler and Gross. The gland has probably a stimulating influence on sexual maturity: we should look for hyperplasia of it at the time of puberty but this has not been demonstrated.

While there have not been reported cases of sexual precocity, associated with tumors of the anterior portion of this gland there are some

which show an *enlargement of the sella turcica.* One of these seen by Beckman was a girl of 6½ who had the bodily development of one of 16, breasts firm and large, axillæ and pubic hair present, mons and labia developed, menstruation irregular. The X-ray showed an enlarged sella. A. Strauch reports a similar case in a boy of 11½ with large penis and testes, pubic hair of female type, axillary hair but none on the face. The sella was enlarged in this also.

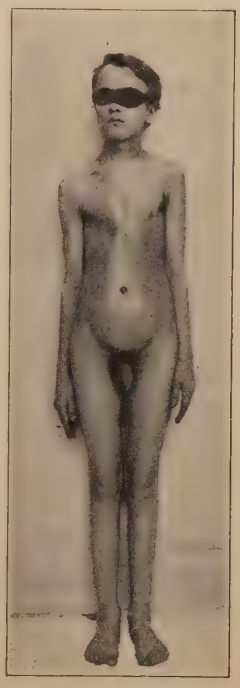

Fig. 2. Case of Dr. A. Strauch. Reproduced by permission of the author from Am. Jour. Dis. Child. 1918. XV. 138. X-ray showed slightly enlarged sella turcica.

Hypopituitarism in adolescents is manifested by a tendency toward persistence of infantilism or at least toward delayed acquirement of secondary sexual characteristics.

Experimental extirpation of the gland from young animals according to Crowe, Cushing and Homans was followed by decided retardation of the growth of the sex glands. Houssay used young dogs and found there was complete arrest or retardation of growth in general and of the teeth, hair and genitalia especially.

It would be inferred from the foregoing that adding anterior portion of the pituitary to the body content would accelerate sexual development. This does occur according to the experiments of Goetsch and others. Goetsch's conclusions, after feeding anterior lobe to young rats are: that it causes increased weight and more vigorous and early sexual development in males and females; that sexual instincts are earlier awakened and breeding occurs earlier and oftener. Histologically the development of testes, epididymes, prostate, seminal vesicles, vasa deferentia, ovaries, tubes and uterus is advanced.

Suprarenal Gland

The suprarenal cortex is derived from the same tissue as the ovaries and testes:—the Wolffian ridge. It might be supposed that changes in the suprarenal cortex would be followed by changes in the gonads. Changes in the secondary sexual characteristics have occurred in cases of Virilism associated with tumors of the suprarenal cortex.

Bullock and Sequiera report the case of a girl, who began to menstruate just before she was 10 years old. Autopsy showed a large hypernephroma of the left suprarenal cortex, enlargement of the right suprarenal and

metastases in the liver and lungs. The uterus and ovaries were enlarged and the latter showed corpora lutea: the thyroid and parathyroids were hypertrophied; no note is made of the condition of the pituitary and pineal bodies. She became fat after menstruation appeared: was 54 inches tall and weighed 87 lbs. The skin was dark but not pigmented in patches. There was a profuse growth of hair on the lip, chin, axillæ and pubis.

Reversive sexual changes have been noticed in adults suffering from tumor of the suprarenal cortex. A. Guemes reports a case of a woman who had a hypernephroma of the right suprarenal cortex and atrophy of the ovaries. Her menstruation ceased early and later she grew a beard. A. Bittdorf (*c*) saw a man of 26 in whom a hypernephroma of the suprarenal cortex was followed by diminution of the sexual desires, atrophy of the testicles and enlargement of the breasts of the female type.

Feeding experiments with this gland have been done by R. G. and A. D. Hoskins. They used white rats with proper controls and fed the animals for two to nine weeks. In them there were found hypertrophy of testicles and ovaries.

I am then inclined to the belief that the suprarenals act as controllers of sexual development. They receive inhibitory or acceleratory influences from the pineal, pituitary gland and thymus.

Gonads

Neurath has collectected five cases of precocious puberty associated with tumors of the ovaries or testes. Since his monograph there has been at least one more, that of Harris. In this case the removal of an ovarian teratoma caused a cessation of the precocious growth and menstruation. In Riedel's case the removal of a sarcoma of the ovaries was followed by a cessation of menstruation. One case of tumor of the testicle associated with precocity is found, the frequently quoted one of Sacchi. This boy grew rapidly until at 9 he weighed 44 kg. (97 lbs.); had hair on the lip, and genitalia; voice deep, penis large, frequent erections and seminal emissions. An alveolar carcinoma of the left testicle was found and removed. After four months the hair on the chin had disappeared; that on the lip and pubes persisted, the voice became childlike, the penis less large, erections and emissions ceased.

The testes consist of two tissues, the interstitial cells of Leydig and the seminiferous tubules of Sertoli. The former seem to be most concerned with the development of the external secondary characteristics: the latter with the development of sexual maturity. One or the other or both may show signs of development with consequent bodily changes. In precocious puberty it is reasonable to presume that both are developed. Such elements in the ovary are not differentiated but from analysis it

may be presumed that they exist. Cushing suggests "the glandular element which is responsible for the physical changes of puberty, differs from that which concerns ovulation and reproduction, and may possibly be a function of specific interstitial cells."

Summary

We have then reported cases of pubertas precox associated with tumors (usually teratomata) of the pineal, hyperplasia of the pituitary (as shown by enlarged sella turcica in röntgenograms) and tumors of the gonads. We may presume to theorize then that the growth in testes and ovaries acts as a stimulant to the interstitial cells and seminiferous tubules: that changes in the anterior pituitary body and pineal send stimulating influences to the suprarenal body and it in turn sends acceleratory influences to the gonads.

Virilismus . . . . . *Henry D. Jump*

Pre-adolescent Group—Post-Adolescent Group—Hirsutismus—General Considerations of Virilism and Hirsutism—Disturbances of Endocrine Glands other than the Suprarenals and the Gonads in Virilism and Hirsutism —Conclusion.

Clinical Syndromes Due to Suprarenal Diseases

Virilismus

HENRY D. JUMP

PHILADELPHIA

Virilismus may be defined as a condition occurring in women and girls manifested by hairiness of the face, body and extremities, and accompanied by somatic and genital changes resembling the male. There is a development of maleness or male characteristics at the expense of the female.

Pre-Adolescent Group

In the cases occurring before the age of puberty there is a premature development of the genitalia with pubic hair of the male type, often an enlargement of the clitoris and lack of development of the breasts. The body grows out of proportion to the age. The most of the cases are obese: some are muscular and strong beyond their years, walking earlier than normal and showing unusual strength. The majority are mentally dull but a few are bright. The voice develops a deep tone. The skin is rough and often the seat of acne: pigmentation is occasionally present but there is never the bronzing, characteristic of Addison's disease. *These children never menstruate.* All of the reported cases died before the sixteenth year. They are poor surgical risks, several having succumbed to minor surgical operations. Ritchie's case died three days after an osteotomy: O. Richard's cases died shortly after tapping for ascites.

The following case reported by Jump, Beates and Babcock is typical of this class. The patient was a girl who died at seven and a half years. She was the larger one of twins, weighing six pounds at birth. She failed to grow normally during the first six months of her life, because of an inability to regulate her artificial feeding. When the proper mixture was found she developed rapidly, gaining eight pounds in two months. Her *growth* continued rapidly until finally she was fifty-three inches tall and weighed about ninety pounds. Her general form was more masculine than feminine and she developed great strength. She was *not obese. Hair* was first noted on her legs and pubes and in the axillæ when she was one year old. At the seventh year it appeared on her arms, lip and chin. At the time of her death the hair of the scalp was long, curly and moderately

coarse: the pubic and axillary hair were like that of an adult: the pubic hair reached the navel, tapering off as is seen in males: there was a growth on the anterior surface of the chest. The beard and mustache were developed as is seen in a boy of seventeen or eighteen. The *skin* was rough over the legs and abdomen when she was one year old and was coarse, red and pimply when she was seven. There was no abnormal pigmentation of the skin. The *genitalia* were developed as in an adult. The clitoris was about one inch long, half an inch in diameter and notched on the under surface. This enlargement was first noticed at about the seventh year. The vagina was small and when the abdomen was opened the uterus, ovaries and tubes were found to be infantile. No testicle was found. She *did not menstruate*. The labia were thick and large. When she began to talk her *voice* was coarser than that of a child and grew deeper until it was a deep bass. While she was still a little girl in many of her qualities, her general behavior was more masculine than feminine. The thyroid was not enlarged. Despite repeated examinations no mass could be detected in the abdomen until she was past seven. At that time there was found a dense elastic mass on the right side extending from the costal border to the pelvis. This grew rapidly and was painless. The tumor was removed about six months after its discovery and was found to involve the whole of the right kidney. There was no line of separation between the suprarenal and the kidney. Microscopically it was found to be a *hypernephroma* of the *suprarenal cortex*. She died three hours after the operation. At the limited autopsy it was found that the left kidney, left suprarenal and pituitary were normal: there were no metastatic growths in the abdomen.

Fig. 1. Virilismus in a girl of 7½ years. Case of Jump, Beates & Babcock. Am. Jour. Med. Sc. 1914. 1. 1190.

It will be noted that the hairiness of the face came late, appearing only just before the tumor was discovered, but that other manifestations of virilismus existed for several years before. Only a small number of these cases have been reported. Those in which careful postmortem examinations were made showed hypernephroma of the suprarenal cortex. The neoplasm was unilateral and acquired in all except one, that observed by Dobbertin, in which the tumor was congenital. The important ones are by Colcott Fox, Pitman, French, Richards, Glynn, Miller, Orth, Dobbertin.

In none of these are there any other constant pathological findings. A few others have been reported in which the description indicates that they are examples of virilismus but the autopsy findings are lacking or incomplete. Such a one is that of Matthew Baillie, who in 1811 described a typical case in which the chief pathological condition was an internal hydrocephalus, but who also had a large tumor attached to the left kidney and adherent to the right kidney.

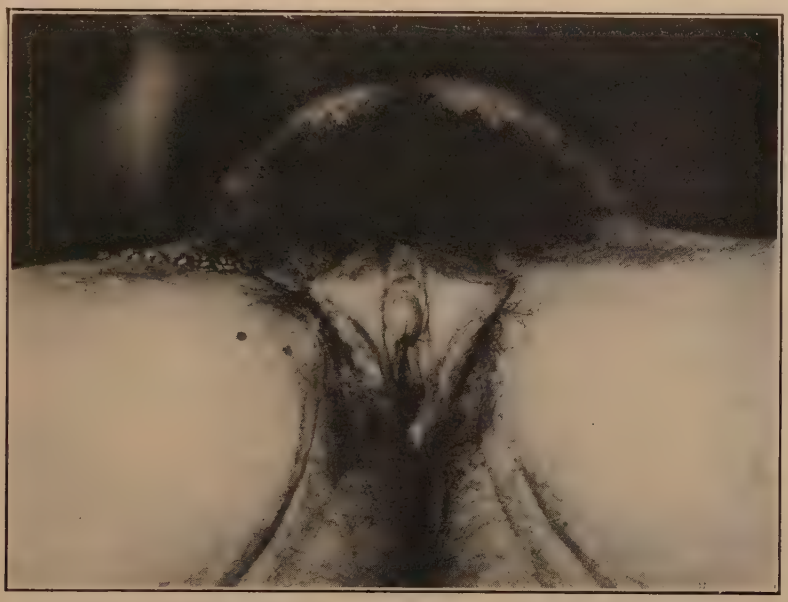

Fig. 2. Genitalia of case in Figure 1. Note the enlarged clitoris.

Hypernephromata of the suprarenal cortex have been found in boys: all of these except one are probably *pubertas precox* for the genital development was described as *precocious*. The exception is that of Guthrie and Emery. The boy of four and three quarter years at death was thirty-six inches tall and very obese, with hair on the face, pubes and back. The genitalia were noted as "not unduly developed." The testicles microscopically were normal and contained no spermatozoa. The thyroid, thymus, pituitary and pineal were normal.

Post-Adolescent Group

After adolescence *virilismus* may occur in women of distinctly feminine type, in whom there has been no doubt as to sex. It is manifested by a cessation of menstruation, atrophy of the breasts, adiposity, coarsening of the voice, growth of hair on the face and body and in some of the enlargement of the clitoris. The hair may grow on the linea alba tapering to the

navel, making the pubic hair assume the male type. In other words, these women develop male characters at the expense of the female just as is seen in the young girls.

A. Guemes reports such a case. The patient's age is not given but from the description she appeared to be about forty-five. Her photograph taken fifteen years before showed her to be of feminine type. Her menstruation, which appeared early, ceased three years before the report was made. The abdomen began to enlarge and she *increased* in *weight* (twenty-six pounds in six months). She became *stronger,* did much hard work and was as energetic as a man: "she feared nothing." The urine showed glucose on one examination. *Hair* then began to grow in unusual places and continued until, at the time of the report, she had a stiff bristly beard and mustache. The arms were covered with hair. The pubic hair was of the masculine type, extending to the navel. The hair of the scalp was gradually lost until she became partially bald. The *voice* became of deep tone. Soon after the appearance of the hair she began to waste and grow weak. The *breasts* shrunk and were covered with dirty wrinkled skin. The *skin* of the face was dry, wrinkled and the seat of pigmented spots. The neck was thick and muscular and contained pads of *fat.* The chest was large and emaciated: the abdomen flaccid and pendulous. The *clitoris* was "exaggerated" and erectile to the slightest touch. There was a rectocele and a cystocele though she had not borne children. The uterus was infantile and the tubes and ovaries impalpable. The thighs and legs were muscular but flaccid and of the conformation of the male. She had a good memory but appeared to be *dull*: was hypochondriacal. Her height was not increased. She had been married twenty years but had never been pregnant and had never had normal satisfaction in sexual relations. At the autopsy there were found *hypernephroma* of the right *suprarenal cortex,* metastasis to the liver, atrophic and sclerosed ovaries, adenoma of the thyroid, sclerosis of pancreas and kidneys.

The syndrome has been observed in cases reported by Alberti and by Zarubin. In one of these the symptoms appeared at twenty and the other at twenty-six after cessation of menstruation. In both the clitoris was enlarged. The former died of an ovarian tumor. The only organs examined at autopsy were the ovaries and uterus. In the other no pathological notes are given. From what we know of such cases it is probable that the suprarenal cortex was the seat of hypernephroma in both of these.

Hirsutismus

Hirsutismus is a condition in which there occurs a growth of hair in unusual places in women beyond the age of puberty. It is characteristic of these cases that they retain their feminine attributes. The milder type of

hirsutismus may be observed in the young woman, who at puberty grows a small downy mustache and in the older woman who at menopause develops a small mustache and also a more or less abundant beard and hairiness of the chest, back and extremities. In these cases there is a lack of evidence of a cause for the condition, except the atrophy of the uterus and ovaries in the older women, and explanation of the cause must depend upon the analogy they bear to more pronounced cases with pathological findings. There is also the more marked type in which the hairiness occurs in association with abnormal growths of the ovaries and suprarenals.

The case of Bovin illustrates the condition which is associated with suprarenal tumor:—A multipara of twenty-one years had gradually ceased to menstruate. There then developed a beard, which necessitated shaving, and an abundant growth of hair on the abdomen. Her general health was good, breasts were well developed and external genitalia normal. When she was twenty-eight Bovin removed a tumor in which the left ovary was imbedded. The microscopical description shows that it was a hypernephroma of an adrenal rest. The right ovary was atrophic and the uterus was like that of a virgin. No note is made of the condition of the suprarenals. Two months after the operation menstruation was reëstablished and continued regularly. Seventeen months later the uterus was of normal size. No change, however, occurred in the unusual hairy growth.

The syndrome has also been associated with tumors both of the ovary and suprarenal. The case reported by Knowsley Thornton is of this class:—A married woman with one child had an oöphorectomy done when she was thirty. There developed soon after the operation a growth of black silky hair all over the body: she shaved her face regularly. When she was thirty-six Thornton removed a tumor attached to the left kidney. The microscopic examination revealed a structure which "reminded the observer of the structure of an adrenal." After her recovery she reported that her external appearance was like that of other women. We understand from this that the hair disappeared. Cases of hirsutism accompanied by hypernephroma of the suprarenal cortex have also been reported by Thummin, Winkler and Goldschwend.

The same condition has been observed in insane women. L. Harris-Liston reports four such. In three of these the hairiness appeared before menopause and in one after it. In all the insanity occurred first. All were in good health except for the insanity and none were mannish. No pathological evidence is offered in these cases. But Linser found in the museum of the Royal College of Surgeons a carcinoma (probably hypernephroma) which completely replaced the right suprarenal. It had been taken from a single woman of thirty-two, who had ceased to menstruate and had a profuse growth of hair on face and legs. She was maniacal and epileptic.

All of these women noted above had normal genitalia and distinct

feminine characteristics, with female type of body and pubic hair. In this particular do they differ from cases of virilismus in which male characteristics develop and the female qualities lessen. The male characteristics are manifested by enlarged clitoris, male type of pubic hair, coarse voices, increased muscular power and hairiness of the face.

Hirsutismus must be distinguished from hypertrichosis, which is a congenital condition and in some cases apparently hereditary. The bearded woman seen in museums probably belongs to this class. L. A. Duhring has given a complete and scholarly description of such a one. This woman had a heavy beard and mustache, patches of hair on the back, chest and extremities. At *birth* there was a fine downy growth where hair occurred later. This disappeared in the first month of life and a few months later was replaced by coarser dark hair. At ten she had a mustache and at sixteen a beard. Her menstruation was normal and she was of a distinctly feminine type. There are no pathological reports available in such cases and we cannot determine what the cause may be.

General Considerations of Virilism and Hirsutism

Virilismus and hirsutismus have many symptoms in common, but so distinct are the differences between them that they must be considered as separate syndromes. As has been noted, the chief characteristic of virilismus is the development of maleness and of hirsutismus is the retention of the feminine characteristics. There are some cases of the latter, which are on the borderline: as for instance the woman of mannish behavior, who has developed a moderate growth of hair on the face at the time of menopause, but shows no other male physical characters: or Thummin's case, who had a deep voice but was of a distinctly feminine type: or Winkler's who had poorly developed mammæ. Apert, Launois, Pinard and Gallais and others do not draw this distinction: they discuss a large number of cases from the standpoint of different manifestations occurring in hypernephromata of the suprarenal cortex. *Tumors* of the *medulla* of the *suprarenal capsule alone are not accompanied by alterations in the secondary sexual characteristics.*

The chief causative factor in both conditions is hypernephroma of the suprarenal cortex. As Glynn has pointed out, it is not the hypernephroma which causes the changes, for such growths occur elsewhere without causing changes in the secondary sexual characteristics. Sarcoma of the suprarenal cortex is not associated with such changes as these. It is probable that hypernephromata cause an increased activity of the cortex and that sarcomata do not. If this be true it is likely that the milder cases of hirsutism, who are usually in good health, have simply a hyperplasia of the suprarenal cortex with increased function.

The changes which occur vary in degree and according to the sex and age of the individual. In boys there is an intensification of their male characters: the body grows, the testicles develop and sexual maturity occurs. In young girls the greater degree of maleness throws the female characters into the background: the ovaries fail to mature while hairiness and other male qualities appear. In older women atrophy of the ovaries occurs and menstruation ceases.

Variations in the development of hairiness, stature, strength, obesity and of the genitalia show the variations in the degree of effects produced.

Disturbances of Endocrine Glands other than the Suprarenals and the Gonads in Virilism and Hirsutism

The alterations which have been found in the thyroid, pituitary and pineal glands associated with abnormal sexual conditions point to a relationship among them in sexual development, which is not understood. What relation they bear to the suprarenals in virilismus and hirsutismus is not clear. In Glynn's case the thyroid was found congested and gave the "impression of overactivity." In other cases these endocrines were not examined or were found normal.

Conclusion:

At the present, we are justified in believing that virilismus and hirsutismus are caused by increased functioning of the suprarenal cortex varying in degree and due in some instances to hypernephromatous growth of the suprarenal cortex.

SECTION III

The Thymus Gland and Its Diseases

Anatomy, Embryology, Comparative Anatomy and Histology . . . . . *E. V. Cowdry*

Anatomy—Size—Gross Morphology and Relations—Blood Supply—Lymphatics—Innervation—Embryology—Origin—Development—Differentiation and Growth—Involution—Variation under Different Conditions—Comparative Anatomy—Histology—The Cortex—The "Small Cells," their Origin and Nature—The Medulla—Mode of Secretion. [From the Anatomical Laboratory, Peking Union Medical College.]

Anatomy, Embryology, Comparative Anatomy and Histology

E. V. COWDRY

NEW YORK

Anatomy

The term "thymus" is apparently derived from two sources. Owing to its bilobed shape, the organ is named after the word "thymus," which is applied to a genus of plants with a two lipped calyx. Galen, bearing in mind its close association with the heart, took the word from the Greek, θυμο, meaning courage.

Size.—The statements of authors conflict with regard to the average size of the thymus gland. When it has attained its maximum development, that it is say at about thirteen years of age, it usually weighs approximately thirty-eight grams, but variations of several hundred per cent are by no means of rare occurrence. There is no reason to suppose that there is any noticeable difference in size as between sexes, as is commonly the case in endocrin organs. The weight of the gland is not always indicative of the amount of thymic tissue, because the proportion of fat and connective tissue varies within very wide limits.

Gross Morphology and Relations.—The thymus is a soft, white, fusiform mass, in which two lobes can easily be distinguished, of which the left is often the larger. It is situated chiefly in the thorax, though it may extend cephalad into the neck region to a variable extent, usually, however, not more than two centimeters. The fourth costal cartilages generally mark its caudal extremity; but it has been known to extend down as far as the diaphragm. Ventrally it is in relation with the sternum, the origins of the sternothyroid muscles, the sternocostal and sternoclavicular articulations, and the internal mammary arteries. Dorsally it comes into contact with the aorta, superior vena cava, and their branches, the pulmonary artery and the pericardium. It is bounded laterally by the pleural sacs and phrenic nerves. A fairly dense capsule surrounds the gland, portions of which penetrate in between the lobules accompanied by vessels

and nerves. The substance of the gland is divisible into cortical and medullary portions. Small fragments of thyroid or parathyroid tissue may be found within the thymus (as in the case illustrated in Fig. 2); and conversely, masses of thymus IV in association with the thyroid and parathyroids.

Blood Supply.—The thymus gland draws its blood supply, for the most part, from the internal mammary arteries; sometimes, in addition,

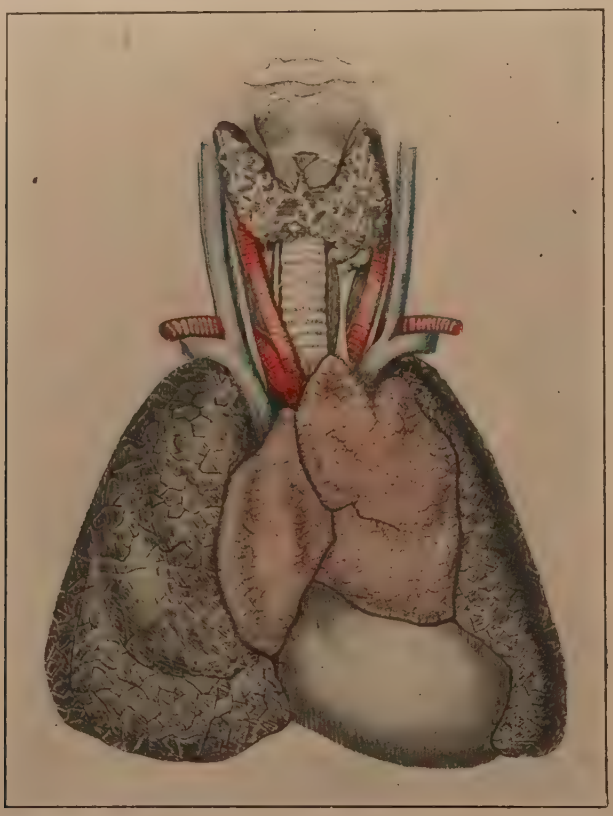

Fig. 1. Thymus gland of full term fetus hardened by formalin injection in situ, after Cunningham.

from the inferior thyroid and pericardial arteries, but there is considerable variation in this respect. A plexus is formed about the center of the gland, from which branches radiate into the surrounding tissue. The blood leaves the organ by numerous venules, which empty into the left innominate vein and sometimes, also, into the internal mammary and inferior thyroid veins.

Lymphatics.—Lymphatic plexuses enclose the lobules and accompany the arteries. The details of their arrangement have been worked out by Matsunaga. The lymphatic drainage from the thymus passes into the

prelaryngeal and cervical lymph glands and into nodes lying dorsal to the sternum.

Innervation.—A few nerves, coming from the cervical sympathetic

Fig. 2. Thymus gland of eight-day-old rabbit with included fragment of parathyroid (p), magnification 720.

and vagus, penetrate the organ with the blood vessels. Twigs from the phrenics and the descendens hypoglossi may enter the capsule.

Embryology.

Origin.—The thymus develops from the endoderm of the third and, occasionally, the fourth branchial pouches, as is indicated by the stippled areas in Fig. 3. The portion, if any, formed from the fourth pouch usually remains in association with the superior parathyroid glands. According to Grosser, the median portion of the third pouch narrows and extends caudally, forming the ductus pharyngobranchialis III, which soon degenerates completely, leaving the thymus anlage free.

Development.—The anlage is at first cylindrical in shape, but the lumen is soon lost, through rapid cell proliferation, and the whole mass migrates in a caudal direction, coming to rest in the cephalic part of the thorax. If the migration is not complete, small portions of the thymus often remain in association with the inferior parathyroids (glandulæ parathyroideæ III). This circumstance makes the results of thymectomy difficult to interpret on account of the uncertainty as to whether all the

thymic tissue has been removed. Each lobe of the definitive thymus is thus formed from a solid cord of cells. Up to this point the gland is entirely epithelial.

Differentiation and Growth.—The growing differentiation into cortical and medullary portions becomes first apparent in embryos of about

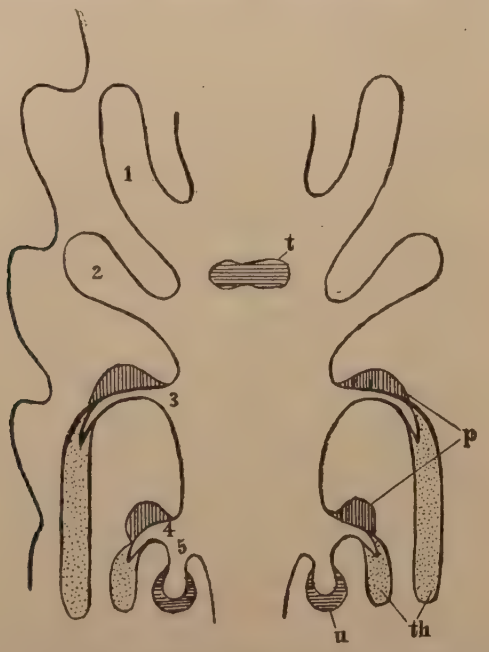

Fig. 3. Diagram showing derivatives of branchial pouches; thyroid (t) and ultimobranchial bodies (u) in horizontal lines, parathyroids (p) in vertical lines and the thymus (th) dotted, after Grosser, modified.

forty-five millimeters. The small round cells become more and more abundant, especially in the part destined to give rise to the cortex. According to Hammar (*b*) (*c*), the Hassall's corpuscles appear in embryos of from sixty to seventy millimeters.

The growth changes are indicated in the following table:

TABLE 2

GROWTH CHANGES IN THE THYMUS GLAND, AFTER HOSKINS, SLIGHTLY MODIFIED

Age in Years	Thymus Weight in Grams	Thymic Parenchyma in Grams	Thymus Per Cent Body Weight	Lymphocytes in Blood Per Cent
Birth	13.3	12.33	.0401	61.0
2.6	23.	19.26	.0162	55.5
9	26.1	22.08	.0090	36.0
14.8	37.5	25.18	.0082	25.0
18.2	25.6	12.71	.0041	23.0
23.3	24.7	4.95	.0037	23.0

At birth the thymus weighs about thirteen grams and has a light pink color, due to its high vascularity. It usually reaches its maximum weight about the time of puberty, when involution begins. Involution may, however, commence before puberty or may be delayed for many years. This general association in time between involution and puberty is not generally found among animals (Hoskins (*b*)). It would rather appear from the table that the decrease in the size of the gland is closely related to the diminution in the number of the lymphocytes in the circulating blood, which is one point in favor of attributing a lymphogenic function to the thymus.

Involution.—The involutionary changes are briefly as follows. The color of the tissue becomes gray, and finally yellowish, owing to the increase in the amount of connective tissue and of fat and the relative decrease in vascularity. The thymic parenchyma decreases in amount, as does all lymphatic tissue, as age advances. This loss is in a measure compensated for by an increase in the fatty tissue, so that the absolute weight of the gland as a whole is not greatly changed.

Variation under Different Conditions.—The growth energy of the thymus is difficult to measure. In rats it is small, since the gland becomes considerably reduced in weight in young animals held at maintenance (Jackson (*b*)). We have evidence also that the weight of the thymus in man is reduced by starvation (Hart (*g*)). Castration is thought to bring about an increase in size and to delay involution. According to Tandler and Gross the thymus is hyperplastic in eunuchs. Feeding thyroid to pregnant animals is said to increase the development of the thymus in the fetus. In very rare cases aplasia, or complete lack of development, of the thymus has been recorded (Clark).

Comparative Anatomy.

A representative of the thymus gland is found as far down the scale as the Lampreys. In some fishes it is claimed that the thymus maintains in adult life the epithelial character, which is restricted to the earlier stages of development in man. In birds, reptiles, and the majority of fishes, however, it is for the most part lymphatic, as in man. Phylogenetically the thymus may be regarded as the descendant of a gland originally pouring its secretion into the alimentary tract, but which has undergone a complete lymphadenoid metamorphosis.

Histology.

The lobes of the gland are divisible into primary and secondary lobules, and in the latter cortical and medullary portions may be distinguished

(see Fig. 4). The space between the primary lobules is usually occupied by loose connective tissue, containing vessels and nerves. In the case of the secondary lobules the dividing trabeculæ do not extend into the medulla in man, though they often do so in lower forms.

The Cortex—The "Small Cells," their Origin and Nature.—The cortex differs from the medulla, in that it is densely packed with small cells, indistinguishable morphologically from lymphocytes. There are two views concerning their origin. According to the first, they are epithelial

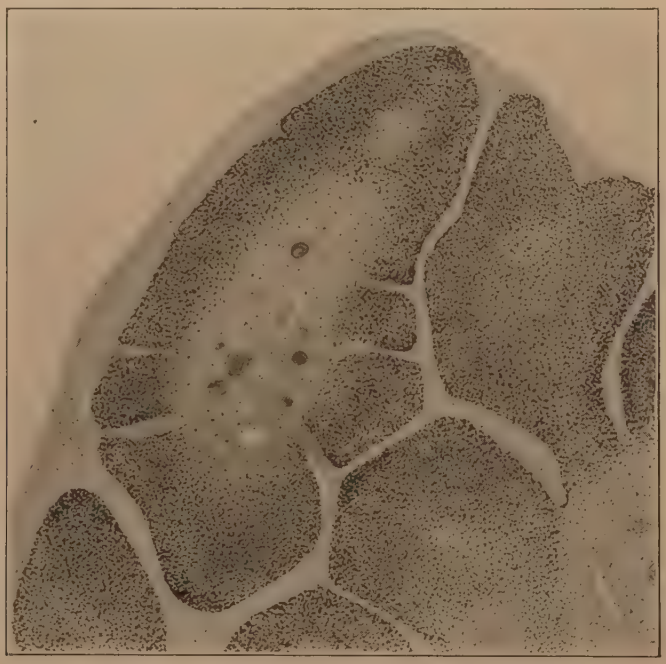

Fig. 4.—Section of human thymus gland (magnification 36).

in nature, arising through the frequent and rapid division of the epithelial cells derived from the branchial pouches. Others, however, consider them to be lymphocytes which have penetrated the organ and greatly changed its appearance. Stöhr has presented some points in favor of their epithelial nature, and Bang claims that the thymus contains five times as great a quantity of nucleinates as lymph glands, and concludes that the cells in question are, therefore, not lymphocytes. Transitional forms between the epithelial cells and lymphocytes, and the occurrence of lymphocytes in the thymus before their appearance in other tissues, are also cited as indicative of an epithelial origin.

It is very difficult to say whether the cells differentiate *in loco,* or migrate into the gland anlage from the surrounding mesenchyme. Contradictory statements are to be attributed, in large measure, to the lack of

specificity of the staining methods. Maximow has made a very careful study of the histogenesis in rabbits, rats, and other mammals. His findings, however, should not be accepted too literally as entirely representative of the human condition. By fixing in Zenker-formol and staining with eosin-azur and Giemsa's stain he obtained a good differential coloration of the lymphocytes, and found that they arise through a differentiation of the neighboring mesenchymatous elements, which wander into the gland. It is highly desirable that it should be ascertained, through the study of the mitochondria and the reticular apparatus, whether there is a discon-

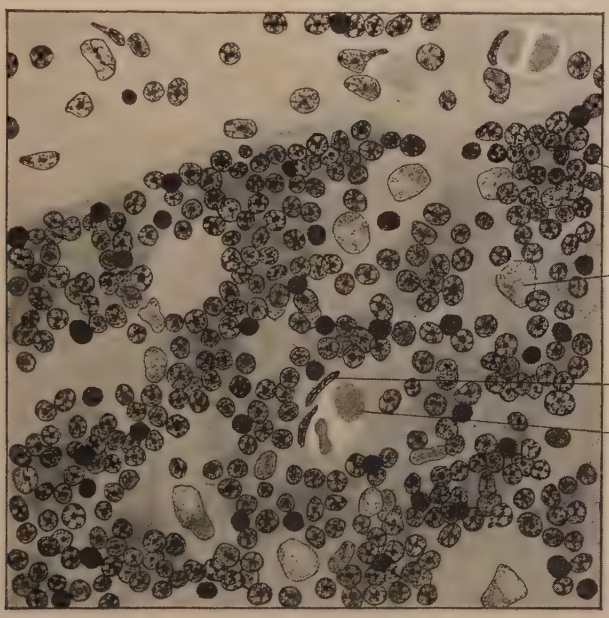

Fig. 5. Section of cortex of human thymus illustrating: Lymphocytes (l), epithelial cells (ep), endothelial cells (en) and erythrocytes (er) (magnification 720).

tinuity between the properties of the cytoplasm of the epithelial cells and lymphocytes.

The small cells of the thymus possess the same basophilic cytoplasm, the same power of ameboid movement, and the same sensitivity to X-rays (Rudberg) as true lymphocytes. Moreover we have reason to believe that they are able to transform into plasma cells and to form granular leukocytes, as do the lymphocytes elsewhere. Neither the small cells nor lymphocytes give the oxydase reaction with α-naphthol and dimethyl-paraphenylenediamin. They are roughly about the same size. On degeneration they undergo similar pycnotic changes. There are no true germ centers in the thymus and it is thought that most of the cell multiplication takes place in the medulla. Prenant is credited with the observation that the details of mitosis in the reticulum (epithelial cells) and small cells are

quite different. The compensatory hypertrophy of true lymphatic tissue following removal of the thymus, as recorded by Basch (*a*), is an interesting argument in favor of the lymphatic nature of the small cells, but requires confirmation.

Cytology of "Small Cells."—The small cells are placed in a reticulum formed by the separation and attenuation of the original epithelium and

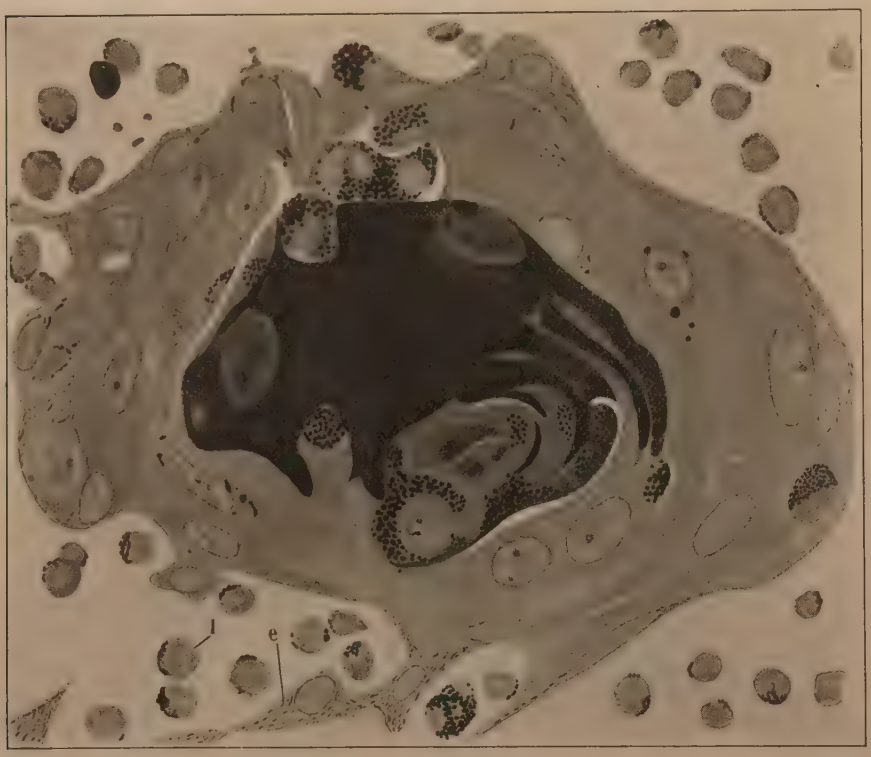

Fig. 6. Hassall's corpuscle in an 8-day-old rabbit prepared to show the mitochondria. Note the difference in the properties of the mitochondria in the epithelial cells (e), and lymphocytes (l); the progressive disappearance of mitochondria as one approaches the center of the corpuscle; and the mode of deposition of the hyaline material (magnification 1500).

the penetration of connective tissue. They contain mitochondria which to all appearances are identical with those occurring in lymphocytes. They present no indications of secretory polarity and no traces of secretion antecedents have ever been found. The nuclei of these small cells are characteristically lymphocytic, possessing a strong affinity for basic dyes. The chromatin is also disposed in the same way in both (Fig. 5).

The Reticulum.—The cells of the reticulum may easily be recognized by their large, pale staining nuclei and by their irregular outlines. Moreover, they contain distinctly smaller mitochondria (e) than the small

cells (1), as may be seen by reference to Fig. 6. Occasionally giant cells are found.

The Medulla.—In the medulla the small cells are less abundant, and for this reason the tissue stains less intensely. The reticular cells occur in rather larger numbers.

Corpuscles of Hassall.—The corpuscles of Hassall are formed through a clumping and degeneration (hyaline, fatty, or colloidal) of the epithelial cells, or of the reticular cells formed from them. Those occupying the center are, judging from the appearance of their mitochondria, either dead or very nearly so. Very frequently the mitochondria seem to give rise to lipoid droplets of variable size. There is a marked deposition of hyaline material. Nuclei are often absent. The corpuscles may become infiltrated with calcium salts. Occasionally they are multiple. Fat is frequenty deposited within them. Bell has shown that they are not always spherical, since they frequently take the form of branching trabeculæ extending throughout the medullary portion of the gland. Hewer claims to have caused their formation in the thymus experimentally through treatment with X-ray. Differential studies on the relative volumes have not yielded much of value, for under normal conditions the corpuscles vary greatly in size and in number. In some animals they are entirely absent throughout life. Small cavities lined with ciliated epithelium are occasionally seen in the medulla, and striated muscle fibers, occurring singly or in clumps, have also been described, but are of very rare occurrence.

There is good reason to believe that the thymus is an organ of blood formation. The small thymic cells are certainly lymphocytes and these, as Danchakoff has shown, possess the power of giving rise to plasma cells and polymorphonuclear leukocytes. The formation of erythrocytes, if it takes place at all in the thymus, is probably restricted to the embryo.

Mode of Secretion.—Salkind's claim that formed secretion antecedents occur within the epithelial cells is interesting, but requires confirmation. According to him, they take the shape of tiny vacuoles, in the center of each of which a deeply staining granule may be seen, suggestive in some respects of the segregation granules of Renant.

Physiology and Experimental Pathology. . . *R. G. Hoskins*

Effects of Thymus Extirpation—Results of Experimental Methods Other Than Extirpation—Conclusion,

Physiology and Experimental Pathology of the Thymus Gland

R. G. HOSKINS

COLUMBUS

The researches of recent years have more and more tended toward a conclusion that the thymus gland has no true internal secretion. In view of the fact, however, that this structure is widely regarded as an endocrin organ, a brief discussion of the evidence seems incumbent.

Studies on the functional significance of the thymus have been directed chiefly to observations upon the effects of extirpating the organ and of injecting extracts of it into experimental animals. Such studies have been supplemented by feeding experiments and by investigations of the morphological conditions in the gland under various conditions.

Effects of Thymus Extirpation

A great many studies upon the effects of thymus extirpation are now to be found in the literature. Apparently, the first investigator to concern himself with the problem was Restelli in 1845. He attempted to remove the gland from 98 animals—sheep, dogs, and calves. Of these, 4 sheep, 1 calf, and 1 dog only survived. All of the animals seem to have been infected, and no significant data resulted from the study (Park and McClure).

Friedleben (1858) published a monograph of 336 pages on the thymus gland. He removed the organ from 3 goats and 15 dogs. The extirpation in the goats was incomplete. In 7 of the dogs it was thought to be complete, and in 5 was known to be only partial. In 3 cases the spleen, as well as the thymus, was removed. The age of the dogs at the time of operation varied from 6 days to 4 months. The results in the goats may be disregarded. Friedleben concluded that the thymus is not essential to life, but that the loss of the spleen and thymus together is necessarily fatal, on account of the resulting disturbances of blood formation. The thymus itself he regarded as having an important function relating especially to blood formation, nutrition and growth. The chief

significance of his experiments is the demonstration that thymus extirpation is feasible. The details of technique which he worked out have been widely utilized by other investigators.

The next important contribution was made by Langerhans and Saveliew (1893). They performed thymectomy on 29 rabbits from 3 to 5 weeks old and on 2 dogs. Three of the rabbits were discarded from the series because the gland was incompletely removed; 6 died of immediate trauma, and 9 within the first twelve days. Nine of the rabbits remained alive and apparently normal for a considerable period. In none of the animals did significant changes result from the thymus extirpation.

Tarulli and Lo Monaco (1897) repeated the thymus extirpation experiments, using puppies and chickens as subjects. In the dogs they noted a decrease in the number of red-blood corpuscles and hemoglobin percentage, as well as a slight increase in the number of leucocytes. These changes appeared within a few days after the operation, but in three or four months the blood again became normal. A retardation in growth was apparent for a month or two, and associated with this was a depression of general bodily strength. The nutrition of the hair also appeared to be interfered with. Such conditions might have all resulted directly or indirectly merely from the incidental trauma. In case of the chickens, no symptoms resulted which could be ascribed to loss of the thymus, per se.

At about this time several investigators made studies of the results of thymectomy in frogs. Abelous and Billard (1896) reported that in their series no frogs survived extirpation of both lobes of the gland for more than two weeks. Within one or two days after the operation the animals showed muscular weakness and gradually developed paralysis, loss of color of the skin, ulcers, progressive anemia, and ultimate edema and death. Transference of blood into a normal animal from an animal reacting to thymectomy caused the development of similar symptoms and ultimate death. Transplantation of a piece of thymus tissue into a thymectomized frog in some cases caused the skin to assume a more normal color but failed to prevent death. Extracts of calf thymus had a similar effect on the skin and resulted in a change from muscular weakness to hyperexcitability. The conclusion was reached that in the frog the thymus is essential to life and the theory was advanced that the organ elaborates a substance which protects the animal from toxins formed in the normal metabolic processes. Camia (1900) was the only investigator who was able to confirm the results of Abelous and Billard.

Ver Eecke (1899) repeated the extirpation experiments and reported the significant observation that proper attention to hygienic conditions prevented the appearance of severe symptoms following the operation. Animals which had developed a considerable degree of the symptomatology described by Abelous and Billard recovered when kept in frequently changed fresh water. It is probable, therefore, that these latter observers

were dealing merely with one of the infectious diseases to which frogs kept in insanitary tanks, and especially those weakened from any cause, are liable. Vincent (1903) found that some frogs at least survived total thymectomy. Some of his subjects lived five weeks without showing any characteristic symptoms. Hammar (1905) reported a careful series of experiments which served finally to convince biologists generally that, in the frog at least, the thymus is not essential to life. He removed the gland from both sides in some cases and from one side only in others. In 16 animals trauma, similar to that incident to thymectomy, was produced but the thymus left intact. In 85 of the animals the experiments were successful. During a period of twelve to fifty-nine days the frogs showed no significant symptomatology.

To return to mammalian experimentation, Carbone (1897) removed the thymus from a series of rabbits and one dog. He was able to detect no significant results except a short-lasting decrease in the number of red blood cells. Ghika (1901) performed thymectomy in 8 cats. In one case only was the operation regarded as complete. This animal became emaciated and died in about a month. In the other cats no characteristic changes could be noted. Cozzolino experimented upon 24 young rabbits, of which 14 survived. No significant symptomatology developed within the period of observation—67 days in the longest case. Subsequently the same author reported the extirpation of the thymus in 2 other rabbits. In these certain bone changes, which were regarded as possibly rachitic, were noted three months after the operation. Shortly after the bone changes appeared the animals emaciated and died. From this time on a great deal of attention was paid to bone changes following thymectomy.

At about this time, also, the relation of the thymus to calcium metabolism was somewhat extensively considered, but without any very convincing results. Fischl (1907) and others studied the problem further in various animals and introduced the idea that thymectomy so much interferes with bone metabolism as seriously to delay the healing of fractures.

One of the most extensive series of thymectomy experiments was reported by Basch from 1902 to 1908. The work of this investigator has been extensively quoted and has to a considerable degree formed the basis of the ideas regarding thymus physiology which have had wide currency for the past two decades. Basch elaborated an operative technique that permitted him to remove the gland with a considerable degree of ease and certainty. His earlier work pertained more particularly to the relation between the thymus and the skeleton. Later he studied the changes produced in the peripheral nervous system. He emphasized the desirability of working on animals as soon as feasible after birth. In 17 out of 20 litters of puppies he succeeded in obtaining at least one control

and one experimental animal which survived the operation for at least a month. In subjects from 14 of these litters bony changes developed which were studied both radioscopically and at autopsy. Within two or three weeks the changes began to be apparent. The bones in the legs of the thymectomized subjects seemed softer and more flexible and the gait became more or less awkward. Later the legs in some cases became bowed or bent to an extreme degree. The bones were more easily fractured in the thymectomized than in the control animals; callus formation was more extensive and subsequent healing processes took place less effectively. These changes suggested to the author that he was dealing with a condition of experimental rickets, but he concluded, on account of the relatively short duration and the generally mild character of the changes, that such was not the case. Basch concluded that the thymus is not a gland indispensable to life, but that it exercises a transitory function during the earlier months of life, when the processes of growth and calcification of bone are most active. As regards the nervous system, he found that the peripheral nerves were more excitable to galvanic current in the experimental than in the control animals. He also frequently noted convulsions. From these findings he concluded that the thymus plays an important rôle in the etiology of tetany. Park and McClure have subjected Basch's data to careful analysis and have concluded that the changes which he reported following thymectomy might be due partially to inadvertent differences between experimental and control conditions, and partly to defective hygienic conditions. They publish a photograph of a young dog which developed a gross appearance very similar to that described by Basch and which was due merely to close confinement.

Results somewhat similar to those of Basch were reported by Soli, MacLennan, Sommer and Flörcken, and Ranzi and Tandler. While the findings were not consistent in details, they were regarded as indicating that the thymus plays a fairly important rôle in the earlier stages of postnatal skeletal development.

The work of Klose and Vogt and of Matti, which more or less confirmed and supplemented that of Basch, has also been very widely quoted and forms the basis of most text-book discussions of thymus function that have appeared in recent years.

Klose, who worked more or less in collaboration with Vogt, has published very voluminously upon the effects of thymectomy. His experimental animals included several species, but his best-known work was done with dogs. The reports of his findings are so inconsistent among themselves and so lacking in specific details as to render an evaluation of them difficult. Klose and Vogt describe the following changes as characteristic of thymectomy. Most striking results were secured when the thymus was removed between the tenth and fourteenth days of life. From two weeks to two or three months after the operation occurred the so-called "latent

period." During this time, however, the tissues seemed to be less firm and the bones somewhat less rigid in the experimental than in the control dogs. Then followed a "period of adiposity." The dogs ate ravenously and became fat. Their intelligence diminished and they became "dreamy and melancholy." This period lasted two or three months. Then followed a stage of cachexia with "thymic idiocy." During this period the dogs were subject to spontaneous fractures and were very liable to different infections. The hair became dry and fell out. The dogs became weak and ultimately died in coma. When the operation was delayed until the third or fourth week the various periods were prolonged. If the thymus was removed as late as the fifth or sixth week, merely transitory symptoms or none at all appeared. In well-developed cases, interference with bone metabolism was marked. The long bones were shorter than normal and microscopically they showed a picture amounting to osteoporosis. Correspondingly the calcium content of the bones was reduced. Experimental fractures were slower in healing in the thymectomized than in the control dogs.

In explanation of their findings, Klose and Vogt evolved a theory that in early life the thymus functions as an organ of "nuclein synthesis." In the absence of the thymus phosphoric acid, or possibly nucleic acid, fails of neutralization and gives rise to acidosis with consequent decalcification of the bones and degenerative conditions in nervous and other tissues.

Matti, in 1913, reviewed the work on thymus function up to that date and reported numerous original observations on thymectomy. His series included 36 puppies and 4 rabbits. All of the rabbits and 6 of the puppies died shortly after the operation. He operated upon the dogs from the eighteenth day to the twelfth week of age. In contrast with Klose and Vogt, he obtained most striking results when the subjects were more than 5 weeks old. The animals were observed from 2 to 10 months. The greater proportion of Matti's experimental series gave negative results. He was content to dismiss these from consideration, however, on the ground that there were probably bits of thymus inadvertently left behind to carry on the functions normally pertaining to the gland. No proof was afforded that such was the case. A few of the dogs developed somewhat striking symptoms. They became weaker and more sluggish than the control animals; the bones became soft and bent under the body weight; finally, the animals became so weak that they were unable to support themselves. The bone changes can be succinctly described as rachitic. Various changes in the different endocrin organs were also observed and on these Matti laid considerable stress.

During the past decade a considerable number of researches upon thymectomy have been published by different observers. Some obtained negative results and others obtained in varying degree such results as

were reported by Basch, Klose and Matti. Pappenheimer (1914) reported the results of a careful research upon rats. In order to prove that the thymus was completely removed, the tissues of the neck and the upper half of the thorax were sectioned serially and examined microscopically. The results were purely negative, definitely proving that in the rat, at least, the thymus gland plays no vital part.

Park and McClure in 1919 published an admirable résumé and analysis of the literature on thymectomy up to that date. To those who are desirous of a more extensive discussion than that herein presented, Park and McClure's paper is especially commended. These investigators added the results of an extensive series of thymectomies of their own. Dogs served as subjects. The thymus was removed from 75 puppies varying in age from 9 days to 7 weeks. The early post-operative mortality was high, so that the series was soon reduced to 24 thymectomized and 19 control dogs from 14 different litters. Each experimental animal had a litter control and, in all but three of the 14 litters, an individual control animal was available. The animals were observed for a period of from 1 to 15 months. Especial attention was devoted to diet and to hygiene. In the whole series of 75 animals the mortality was 13 per cent greater in the experimental than in the control dogs. Of the thymectomized dogs that failed to survive, 82 per cent died within two months, i. e., within Klose's "latent period" when thymectomy per se was supposed to give no serious results. Considering the necessary severity of the operation, the striking feature of these findings is that the mortality was so nearly the same in the experimental and in the control animals. With one possible exception, the authors were able to offer plausible explanations other than deprivation of the thymus gland for the sickness and death of all the thymectomized dogs. Ten of the thymectomized animals remained well throughout the course of the experiment; they were observed from 7 to 15 months. The authors were unable to determine that the operation resulted in any significant depression of growth or development. Neither did the thymectomy result in rickets or any skeletal disorder. The thyroid, suprarenals, and testes or ovaries were essentially alike in both the normal and control series. The authors conclude definitely that the thymus gland is not essential to life. Thymus function plays no necessary part in the process of ossification. Neither is it essential for the normal growth and development of the hair, teeth, and muscles, nor for normal intelligence. The possibility, however, that thymectomy may cause delayed closure of the epiphyses was not entirely excluded.

As a result of their own studies and of the analysis of the literature, Park and McClure point out that "there are other explanations than deprivation of thymus function for the symptoms and pathologic changes which have been reported in thymectomized animals. and that those ex-

planations must be seriously considered in the interpretation of all positive experimental findings, and that for the interpretation of the positive experimental findings reported by some investigators those explanations become absolutely essential." On the whole, the available evidence from extirpation experiments quite fails to prove that the thymus has any endocrin function.

Results of Experimental Methods Other Than Extirpation

Several observers have studied the effects of grafting thymus tissue into other animals. These investigations have been directed particularly to forestalling the assumed deleterious effects of thymectomy. If thymectomy, however, has per se no deleterious effects, such researches of course fall to the ground. At any rate, grafting experiments have failed to contribute anything significant to our present-day knowledge of thymus function.

Relatively few investigators have studied the effects of thymus feeding in mammals. E. R. Hoskins (1916) reported completely negative results in rats. Gudernatsch's experiments with tadpoles have been widely quoted. Later investigations seem to indicate that Gudernatsch's results were due merely to the food factor. For a fuller discussion of the results in amphibia, the chapter on "Endocrin Factors in Growth and Development" may be consulted.

Injection experiments also have failed to contribute any significant data on thymus function. Thymus extracts, when injected into the bloodstream, give merely such reactions as can be obtained from non-specific tissue materials in general (Vincent and Sheen).

Much stress has been laid on the early postpuberal involution of the thymus, as indicating that this gland plays an important rôle in bringing about the changes characteristic of puberty. As Hammar has pointed out, however, involution occurs to a much less extent than is often supposed. While it is true that the thymus weight in adults, as reported in the literature, is relatively much less than in youths, this can be accounted for to a considerable extent by the fact that the data had been derived from autopsies following death from various wasting diseases. The thymus, being especially liable to inanition atrophy, is in such cases much below the normal adult weight. When the glands are collected from subjects who have died suddenly in a state of good nutrition, they show to a very considerable degree the same morphological structure as in youth. Whatever function the thymus may have, therefore, probably persists well past the puberal stage.

Conclusion

The literature as a whole affords little or no reliable evidence that the thymus has any true endocrin function. In all probability the organ is of significance in the physiological and pathological processes merely by virtue of its lymphoid character. Whatever function it has probably is concerned with the defensive mechanisms against infections. Such an aspect of thymus function obviously does not fall within the purview of this work.

Pathology of the Thymus . . . . . *Andre Crotti*

Thyroid Aplasia and Hypoplasia—Pathological Involution or Atrophy—Active and Passive Congestions—Hemorrhage—Acute Thymitis—Acute Infections and Thymus—Tumors—Benign Thymomata—Malignant Thymomata—Sarcomatous Thymomata—Carcinomatous Thymoma—Mixed Malignant Thymomata.

Pathology of the Thymus

ANDRÉ CROTTI

COLUMBUS

Thyroid Aplasia and Hypoplasia.—According to several authors, absence of the thymus, or even thymus hypoplasia, are causes of mental disturbances in children. In 28 mentally defective cases Bourneville found the thymus absent. Basing his conclusions upon a large number of autopsies of mentally defective children, he found that in 70 per cent the thymus was absent. Although not contending that any one type of case can be referred to the deficiency of one organ, Sajous (*b*) believes that the deficient activity of the thymus results in deficiency of nucleins supplied to the brain through the lymphocytes, thus causing idiocy. Harrower (*c*) makes the statement that thymus hypoplasia is found in conjunction with defectiveness and with a hypoplastic type of individual.

Pathological Involution or Atrophy.—There are two forms of involution, the *physiological* and the *pathological.*

The physiological involution belongs to the chapter on Physiology.

Pathological involution may occur without any apparent cause or may occur in conjunction with chronic conditions or infections such as marasmus, tuberculosis, empyema, etc. This pathological involution is most likely due to some intoxication or irritation centering upon the thymus. Adipose cells disappear; the arteries and veins show signs of endarteritis, and the cortical and medullary substances are no longer easily differentiated. The lymphoid cells are more or less absent and are replaced by fibroblastic and endothelial cells resembling, in many respects, those found in the Hassall's corpuscles. The eosinophiles are diminished. The Hassall's corpuscles are somewhat increased in size and number, but show retrogressive changes.

Atrophy may become so marked as to obtain a complete sclerosis of the thymus.

Active and Passive Congestions.—(*Edema and Hemorrhage.*)—Active and passive congestions of the thymus may occur under the most varied conditions; as a result, the thymus becomes enlarged and reddened. Such a congestive enlargement may be mistaken at autopsy for a real thymic hyperplasia. There is no doubt that such congestions play a very prominent part in suffocation due to thymic hyperplasia and to other reasons.

Usually such a congestion can be easily detected at postmortem; it may have disappeared entirely, however, the gland appearing to be absolutely normal.

Edema of the thymus may be observed not only in generalized edema, but in localized conditions also, such as infections of the walls of the chest, and of the mediastinal space. When large saline injections are given in the pectoral region, just before death, marked edema may be found in the thymus.

Hemorrhage.—(1) *Hemorrhagic Cysts of the Thymus.*—This condition was first called by Friedleben, "apoplexy of the thymus." It usually occurs in the newborn. It is characterized by sudden hemorrhages taking place in the thymus. It is not a parenchyma hemorrhage, but is a bleeding taking place in a preformed cavity composed of a wall with a distinct lining membrane, whose epithelium is usually flat, but which sometimes happens to be cylindrical, thus suggesting that the cystic cavity is due to remnants of thymic ducts. A coincidence of remarkable significance is that these hemorrhages occur usually in conjunction with congenital syphilis. At least, the cases reported by Barensprung, Ritter and Raudnitz, Schlesinger, Mendelsohn, Bednar, and Sultan, were all syphilitic cases. Is there a relation of cause to effect between these two conditions? This is very probable, and most likely the immediate cause of the bleeding is due to the rupture of some blood-vessel caused by luetic endarteritis.

(2) *Diffuse Hematoma of the Thymus.*—This takes place in older children and in adults as well, and usually occurs in conjunction with acute diseases, although it may happen without any apparent cause. The hematoma is not limited by a well defined membrane as in cystic hematoma, but permeates diffusely the thymic tissue, involving a greater or lesser portion of it. In rare cases the whole thymus has been found involved; it appears then like a total infarctus of the gland.

(3) *Punctate Hemorrhages of the Thymus.*—Small punctate hemorrhages are frequently observed in the thymi of new-born and of young children dying from acute infectious diseases as whooping cough, pneumonia, hemophilia, convulsions, sepsis, etc. Dudgeon found hemorrhages in the thymus in 95 per cent of the deaths following bronchopneumonia and lobar pneumonia. The same type of hemorrhage is observed, too, in cases of difficult delivery especially in malpositions of the fetus followed with rotation, and forceps application. Attention to these cases was called by Weber in 1842, and since then various obstetricians have reported similar cases. Hemorrhage in such cases is characterized by a rather punctiform aspect involving the whole gland and extending to the neighboring structures, such as the pleura, pericardium, etc. The hemorrhagic point, however, may be as large as a pea, or larger. Under such conditions the thymus is much enlarged, has a firm consistency, hence, pressure

upon the trachea and upon the mediastinal organs, hence, suffocation. Syphilis in these cases is not an etiological factor.

In 1909, Winkler reported a case of a four days old child who had undergone a forceps delivery, and who died four days after birth with symptoms of suffocation, although he had been apparently well up to that time. Postmortem showed a large hematoma of the thymus caused probably during the delivery. Another hematoma was observed in the right cerebral hemisphere, thus showing that the mechanical origin of the thymic hematoma was very probable.

Acute Thymitis.—A primary thymitis has not yet been reported. The very rare cases so regarded are doubtful. On the other hand, acute thymitis, secondary to metastatic infections following some other acute focal process, has been observed more than once. Schridde, for instance, reported an abscess of the thymus following a retropharyngeal abscess. The same was also observed by Hutinel and Tixier, Roger, Ghika, and Klein after diphtheria and syphilis.

In 1914, McWalter reported a case of acute thymitis in a child, twelve months old, who had previously been healthy. Within the previous eight days, however, he had developed a swelling at the suprasternal notch which extended upward as far as the hyoid bone and spread laterally as far as the middle third of the clavicle on each side. There was a distinct dullness over the upper part of the sternum. The swelling was uniform, smooth, homogeneous, not hot, and not painful to the touch. There was some redness of the skin, but no sign of suppuration. The child suffered from dyspnea. The appearance of the child, rather than the gravity of the symptoms, alarmed the mother. A solution of oil of wintergreen in almond oil (20 per cent) was applied to the swelling and rapid improvement had set in, when suddenly the child ceased to breathe and death occurred suddenly and painlessly about the fourth day of the treatment. Here the absolute proof, namely postmortem, that this case was really an acute thymitis, is lacking.

The organisms most frequently found in thymic abscesses are the staphylococcus, the streptococcus, and the colon bacilli. Metastases take place through the hematogenous route. Localization of the abscess may take place either in the parenchyma or in the existing cysts. Diagnosis in these cases is made by taking into consideration the pressure symptoms due to tracheostenosis, the temperature, pressure-pain upon the sternum, leukocytosis, and polynucleosis. X-ray may be of great value. These abscesses are usually located in the mediastinal portion of the thymus; any surgical attempt to relieve the patient is consequently difficult and dangerous. It is, however, the only possible means of giving the patient relief.

Acute Infections and Thymus.—That the thymus undergoes hyperplasia in acute infections was already noticed in 1847 by Herard, who based his conclusions upon sixty postmortems.

In 1858, Friedleben reported that the thymus in acute infections becomes, on the average, about three times larger than normally, whereas in chronic conditions it undergoes a marked atrophy.

In 1888, Jacobi made a microscopical examination of nine cases who died from acute infections such as diphtheria, bronchopneumonia, and in two cases only did he find necrobiotic changes in the lymphocytes.

In 1894, O. Hausen reported observations obtained from 16 postmortems, the cause of death being diphtheria. He found an enlarged thymus in each case.

In 1894, Mettenheimer examined 13 cases of diphtheria and 5 cases of scarlet fever and came to the conclusion that in acute infections the thymus undergoes involution instead of hyperplasia. Microscopically, he found hyperemia of the thymus and did not find the same degenerative changes of the cells, such as described by Jacobi.

In 1900, Roger and Ghika made some experimental researches to see how the thymus reacted toward infections and at the same time examined the thymi of patients dying from acute infectious diseases such as scarlet fever, varioloid, diphtheria, erysipelas, pertussis, tuberculosis and syphilis. Experimentally, by injecting in guinea-pigs virulent cultures of streptococci, staphylococci, colon bacilli, and Löffler bacilli, they were able to produce the same pathological changes as observed in acute infections, i. e. hyperplasia of the thymus, congestion, punctate and subcapsular and intracapsular hemorrhages. Microscopically, they found the walls of the blood vessels infiltrated with leukocytes and showing some hemorrhagic foci. The lymphocytes were quite numerous especially in the medullary portions. Mono- and polynuclears, eosinophiles, neutrophiles, mast cells and giant cells were observed. Hassall's corpuscles were increased in size and number and showed some retrogressive changes.

In 1901, Magni made cultures of the thymus of children who died from acute infections and was able to obtain positive cultures. It is his opinion that the thymus is more frequently invaded by microbes than the liver, spleen, mesentery, etc.

In 1903, Francesconi studied experimentally the influence of microbic infections upon the thymus of guinea pigs and found that the gland becomes hyperplastic, that the lymphoid elements, especially the medullary portions, become markedly increased, showing karyolytic changes, and that the endothelium of the blood vessels is swollen and the connective tissue is infiltrated with leukocytes.

In 1904, Mensi repeated the same experiments and found that in 11 cases out of 26, the bacteriological examination of the thymus was positive. In 22 out of 26 cases the Hassall's corpuscles were markedly increased in size and number and the eosinophiles were also increased.

Bracci, in 1904, studied the relation of the thymus to infections and observed that the Hassall's corpuscles underwent degeneration and that

they were more or less transformed into small cystic nodules. At the same time, Hassall's corpuscles were increased in number and size, so much so that some of them were confluent and fused together to form a cavity. The connective tissue underwent a sclerotic process. The parenchyma was separated by void spaces of various sizes.

In 1905, Fortescue and Brickdale examined 20 cases of children who died from acute diseases such as pneumonia, diphtheria, peritonitis, etc., and found that in some cases involution of the thymus was present while in some others hyperplasia had occurred.

In 1909, Ronconi, examining two cases of diphtheria, found an increased volume of the thymus and increase in the number of Hassall's corpuscles. Some of these corpuscles showed retrogressive changes.

In 1910, Marfan (*c*), examining the thymus of patients who died from diphtheria, erysipelas, variola, infectious purpura, etc., found thymic hyperplasia with increased number and size of Hassall's corpuscles and eosinophiles. The same findings were reported by Pappenheimer (*a*), in 1910. Holdström reported the same findings in 1911.

K. Takeuchi (*a*) studied experimentally the reaction of the thymus to acute infections in 57 rats, which were injected with colon bacilli. He did not observe, as is usually the case in human beings, any inflammatory hyperemia and hemorrhages of the thymus. He noticed that the cortical and medullary substances lost their well established differentiation. The thymic cells, at first, became hyperplastic, then showed degenerative changes and resorption, so much so that in the last stage there remained practically only connective tissue and Hassall's corpuscles. He did not observe any increase in the number and size of Hassall's corpuscles and of the eosinophiles, as happened in thymic infections in human beings.

In 1912, Hart basing his conclusions upon 100 cases, reported the same findings, namely, in a great number of cases an increased hyperplasia of the thymus, increase in size and number of the Hassall's corpuscles, and increase of the eosinophiles. In diseases of long standing and of severe type, the damage done to the thymus is irreparable; pathological involution takes place, connective tissue infiltration invades the thymus after which a fatty degeneration takes the place of the thymus.

In 1914, Oliari examining the thymus of 25 individuals who had died from various diseases such as tuberculosis, pleurisy, pneumonia, etc., observed hyperplasia of the thymus, sclerosis of the gland, and in a general way, marked regressive changes.

In 1918, Hammar reported the results of his researches of 21 cases that died from diphtheria and came to the conclusion that in diphtheria the thymus undergoes an accidental involution in which more or less marked regressive changes are observed, but in which the number and size of Hassall's corpuscles are increased.

Furthermore, in examining the relation of the thymus to infectious diseases such as acute anterior poliomyelitis, measles, scarlet fever, pertussis, typhus, typhoid, etc., Hammar, in 1918, observed that the thymus in a general way showed an increase in size and number of the Hassall's corpuscles. In diseases of long standing such as chronic tuberculosis, etc., the thymus underwent an involution, but no increase in size and number of the Hassall's corpuscles was observed. The same is also true in the case of hunger.

In conclusion, we may say that the thymus reacts towards infectious disease mostly by an increased blood supply, by hyperplasia of the thymic elements, and by hyperplastic changes taking place in the Hassall's corpuscles. In some instances, however, pathological involution, instead of hyperplasia, takes place.

Sclerosis of the Thymus.—In certain cases of malnutrition, of syphilis, and of tuberculosis, the thymus undergoes a process similar to the one observed in atrophic cirrhosis of the liver and kidney. There, too, as in the latter conditions, we have a process of connective tissue formation, gradual in character, involving the cortical substance first and the medullary portion of the thymus afterwards. In the terminal stage all that remains of the thymus is a small but hard mass involving the whole gland and firmly attached to the neighboring tissues. This sclerosis of the thymus in many respects resembles the one seen in the thyroid and called "woody thyroiditis." In rare cases, as reported by Klose, the production of connective tissue is so great that this author is inclined to regard these cases as fibromata.

Syphilis of the Thymus.—Nothing is known of secondary syphilis so far as the thymus is concerned.

Tertiary syphilis has been found once in a while and is characterized by gummata, which do not differ in any way from those seen in other organs.

In hereditary syphilis Paul DuBois, in 1850, described abscesses known since in the literature as "DuBois abscesses." They are not abscesses in the true sense of the word, but are due to the breaking down of a syphilitic gumma. Some pus is usually found. They always contain a large amount of spirochetes.

Chiari (*a*) (*b*), in 1894, studying several of these so-called "DuBois abscesses" in the new-born, found on microscopical examination that these abscesses were surrounded by a capsule composed of several layers of cells plainly keratohyalin in character. He concluded, therefore, that these abscesses originated in previously existing cysts. The contents of these cysts was composed of cells with large, clear nuclei, and small lymphoid cells. The keratohyalin character of the cells led him to conclude that the cyst took its origin primarily in a Hassall's corpuscle.

Tuberculosis of the Thymus.—Primary tuberculosis of the thymus is

vary rare. The majority of cases reported are doubtful because enough care has not been taken to ascertain if the primary focus was in the thymus, in the tracheobronchial glands, or in the lungs. About the only case of undoubted primary tuberculosis of thymus is the one reported by Demme, that of a child whose parents were non-tuberculous, and who died in the third month of general marasmus. Autopsy showed an enlarged thymus containing several tuberculous foci. No other evidence of tuberculosis could be found anywhere else.

Secondary tuberculosis of the thymus is more frequent, however, as a number of cases of tuberculosis of the thymus following a primary process located in the neighboring organs as the tracheobronchial glands, lungs, etc., have been reported.

In 1888, Jacobi (*b*) examined about 100 thymi of tuberculous patients. In his judgment, tuberculosis of the thymus is not so uncommon since he found it 3 times out of 60 cases in patients having died from any kind of disease, except tuberculosis and found it in one-fourth of all the cases that died from tuberculosis. Tuberculosis occurs as a military or as a caseous form. In all the cases he was able to demonstrate the presence of tubercle bacilli.

Carpenter reported the autopsy of a child, two years old, in whom a large tuberculous abscess was developed in the thymus gland. Tuberculosis had involved both lungs. In this case it is impossible to determine whether the tuberculosis was primary in the thymus or only secondary. The latter alternative seems the more likely.

In 1909, Tixier and Feldzer performed an autopsy on a child, three years old, who had died of pulmonary tuberculosis. Autopsy showed that the tuberculosis had involved the lungs, the tracheobronchial glands, liver, spleen, and kidneys. None was found in the brain. The thymus was studded with tuberculous abscesses. In another child, one year old, another bilateral tuberculosis of the thymus, caseated in type, was found. The tracheobronchial glands were heavily involved. Microscopical examination, however, showed that the thymus in places had undergone connective tissue formation, that congestion was very marked, and that the Hassall's corpuscles had almost entirely disappeared. In another child, ten years old, the left thymus was almost entirely caseous and the center contained a great amount of pus. The right lobe was free from tuberculosis. The microscopical examination of the right lobe showed that the differentiation between the cortical and the medullary portions had almost entirely disappeared, that sclerosis was quite advanced in the non-tuberculous portion of the left lobe, while not so marked in the right one. Hassall's corpuscles were very scant in the portions to the thymus involved by the tuberculosis. In a twenty-seven months old child, who died of bronchopneumonia following whooping cough, the thymus was found involved by tuberculosis. The connective tissue was markedly developed,

the cells of the thymus were polymorphic in character, and the Hassall's corpuscles were mostly absent. In another child, nine months old, the tracheobronchial glands were tuberculous. There was at the same time a small cavern in the right lung. The thymus was caseous. The sclerotic portions showed a marked polymorphism of the cells and a diminution of the Hassall's corpuscles. In all these cases examined, the presence of tubercle bacilli was made certain.

Tuberculosis of the thymus may affect the miliary or the caseous type. In miliary tuberculosis it is not uncommon to find a few small tuberculous nodules throughout the thymic parenchyma. These tuberculous nodules have no special significance except that they are only one phenomenon of a generalized process.

As seen in reviewing the literature, primary caseous tuberculosis is very rare. Secondary caseous tuberculosis is more frequent. It is found in connection with caseous tuberculosis of the mediastinal lymphnodes. Often, however, in very advanced caseation of the mediastinal lymphnodes, one is rather surprised to find the thymus absolutely untouched.

In leukemia and in Hodgkin's disease, the thymus seems to be usually uninvolved, although the mediastinal lymphnodes may be very hyperplastic.

Tumors

Primary tumors of the thymus are not as rare as they would at first seem to be. As in many other organs, we find in the thymus, benign and malignant tumors.

Benign Thymomata.—A *lipoma* has been reported by Wadde, Münchmeyer, and Müller. A *myxoma* was described by Winogradow.

Fibroma.—In 1909, Winkler observed a case of atrophic cirrhosis of the thymus in a thirteen-year-old child. The tumor was a large mass, 22½ cm. wide, 9.8 cm. long, and about 2 cm. thick, hard, nodular in surface, and attached to the neighboring tissues. The mass was removed by operation after making a partial dissection of the sternum. It was composed of connective tissue, more or less well organized, containing foci of lymphocytes and fatty degeneration. Small, round figures resembling Hassall's corpuscles were observed. Winkler regarded this as a fibroma.

Dermoid cysts are rare. They may be uni- or multilocular, and contain hair. No other foetal tissue is found.

Cysts.—Thymic cysts are rather rare. Two great varieties are found: 1st, the ciliated cysts; 2d, the cogenital syphilitic cysts.

The ciliated cysts are present in human beings as well as animals. They are lined with cylindrical, ciliated epithelium and are found in fetus and new-born. They are usually located in the same portion of

the gland, namely, in the superior pole and in the cortical substance. That this is not always the case, however, has been proved by Pigache and Beclere, as shown later.

It was Remak, who, in 1855, was the first to notice the existence in the thymus of cysts lined with ciliated epithelium in cats. Watney, in 1883, observed them in dogs, Capobianco (*a*) (*b*), in 1892, in the cat, Tourneux and Verdun, in 1897, in human fetuses, Von Elner, in 1902, Hammar (*a*), in 1905, in the cat, dog, chicken, and frog. Dustin (*a*), in 1909, observed them in the thymus of lizards. In 1896, Nicholas found ciliated cysts not only in the thymus, but also in the parathyroids.

Pigache and Beclere, in 1911, observed similar cysts in a dog, two rabbits, and a mouse. These cysts were nearly always found in the medullary portions of the thymus. They were extremely irregular in character and the cells which constituted their lining were in turn cylindrical, cuboidal, or pavimentous. These three forms of epithelium were usually combined in the same cyst. Many of these cells were ciliated, but by no means all of them, and the ciliated ones were disposed in a very irregular way. The lumen of the cyst contained a mass of cellular detritus showing all stages of degeneration.

In adults, cysts of the thymus are very rare. Hueter, however, reported a very interesting and unique case of a large cystic formatior in an adult. The tumor was 76 mm. long and 28 mm. wide. It was polycystic, resembling in every respect a bunch of grapes. The tissue between the cysts was absolutely normal and contained a great many Hassall's corpuscles. The connective tissue was more or less marked and sclerotic. In the cyst itself polypoid arborescences and cholesterin were present. Nothing suggestive of malignancy in these cysts was present. Similar observations have been made in animals.

Hueter observed small thymic cysts in individuals between eighty and ninety years of age. No syphilis was present. These small cysts were the size of a pea, contained a great deal of cholesterin and were located in a fatty mass supposed to be the thymus. That it was really so, was revealed by the fact that the microscope showed the typical structure of the thymus.

Chiari (*a*) (*b*) thinks that congenital cysts are due to cystic degeneration of Hassall's corpuscles. Eberle thinks they take their origin in unobliterated segments of the excretory canals of the thymus. Tuve believes that the cysts are of syphilitic origin and are formed by necrosis of parenchyma becoming surrounded by an inflammatory zone which is finally converted into a thick capsule lined with a low cuboidal epithelium.

Congenital Syphilitic Cysts.—These cysts are lined with a squamous cell epithelium and contain a great deal of more or less degenerated cellular tissue and frequently some pus. They are often known as "Dubois abscesses." (See Syphilis of the Thymus.)

Malignant Thymomata

Malignant tumors of the thymus may be classified in two large groups: those belonging to the family of sarcomata, and those belonging to the family of carcinomata. The ones most frequently found are the sarcomata; they take their origin in the connective tissue of the thymus. The lymphoid cells of the cortical substance are capable, too, of giving rise to sarcoma, hence, the name, lymphosarcoma. This is the most common form.

The pure carcinomata are much more rare, whereas the mixed tumors are more common. The thymic carcinoma occurs in a rather advanced time of life, while the lymphosarcoma occurs in an earlier period.

The lymphosarcoma was called by Grandhomme, in 1900, thymoma. The coining of the word is a happy one, insofar as it designates the organ involved, but it does not give any information as to the nature of the tumor. Indeed, a thymoma may be benign or it may be malignant. If malignant, it may be sarcomatous, or carcinomatous, or both together. Hence, we ought to say a carcinomatous thymoma, a sarcomatous thymoma, etc.

There is great confusion in the nomenclature adopted by the writers, some describing as sarcomata tumors regarded by others as carcinomata, and vice versa. The reason is because there is such great difficulty in dividing sharply every variety, and because the differences between carcinoma and sarcoma are sometimes very scant. This confusion is due, according to Ambrosini, to the great polymorphism of the thymic cells, of the lymphocytes, of the reticular cells, of the giant, plasma, and eosinophile cells. Their interrelation produces a histological picture very similar to the one of Hodgkin's granuloma, hence, according to Ewing, "the great majority of thymic tumors and especially of mixed growths, represent infectious granulomata, or particular forms of cell growths on the basis of the infectious granuloma. This, from the etiological point of view, offers a simpler explanation for the great variety of structural forms which thymic tumors present."

The sole criterion that one may accept for the diagnosis of tumor of thymic origin is the presence in that tumor of Hassall's corpuscles. If, however, polyhedral or giant cells are present then the probability of the thymic origin of these tumors becomes more certain, because according to Ertmann, Weigert and Lacquer, these large cells are most likely of reticular origin.

In surveying the literature of the cases so reported, only a few can be accepted as primary tumor of the thymus. The majority of the cases reported are most probably of thymic origin but not absolutely beyond doubt.

As a general principle, malignant thymomata of the thymus grow slowly. This, however, is not always the case. Ambrosini saw five cases which were fatal in from two to nine months. I saw one case fatal in ten months and another in two years.

On account of the location of these thymomata, pressure takes place not only upon the trachea, but also upon the esophagus, the base of the heart, the arteries and veins of the mediastinal space, upon the vagus, the recurrent pharyngeal, and the phrenic nerves. In a later stage, however, the tumors involve the pleural cavity and the lungs.

Metastases in the thymus of malignant tumors of other organs seldom take place.

Sarcomatous Thymomata.—These tumors are generally soft, although some are found showing general fibrosis of the tumor. The surface is usually smooth; in rare cases it is found to be nodular. Local softening of the tumor due to necrosis is not frequently observed. Usually, although at first strictly encapsulated, these tumors in a later stage become adherent to the neighboring tissues, invade the organs and spread throughout the entire mediastinal space and the neck. The lymphnodes first involved are the peribronchial. Metastases are very frequent in the axillary and cervical lymphnodes and occasional metastases are observed in the distant organs, as the spleen, pancreas, kidney, liver and adrenals, as reported by Zininiewicz, and finally in the bones and muscles. That sarcomatous thymomata should finally corrode and perforate the sternum is not a characteristic property of theirs. Any malignant tumor of the chest and any large aneurysm of the aorta can do so.

The microscopical picture of the thymic lymphosarcoma does not in many instances differ very much from the one of granuloma malignum. Sometimes, the only difference between the two conditions is the presence of Hassall's corpuscles.

On close examination, the round cell tumors of the thymus, according to Ewing, are found to differ little in structure from the round cell tumors of the lymphnodes. The lymphocytes are few. The chief cells showing mitoses are rather polyhedral in shape, with acidophile cytoplasm, vesicular nuclei, and well developed nucleoli. They often cling to the walls of the numerous small capillaries where they assume a cubical or even cylindrical form. They frequently produce abortive Hassall's corpuscles. Still, according to Ewing (*a*), the giant cells are of two main types:

1st, the poor-staining reticular cells with their irregular contour and containing vacuoles and red-cell detritus.

2nd, the myeloid giant cells with opaque acidophile cytoplasm and many vesicular nuclei. These giant cells do not look like the smaller giant cells of Hodgkin's disease. Increased connective tissue formation is usually present.

Spindle-cell sarcoma has been encountered; it takes its origin from the connective tissue of the thymus gland. Such a case was reported by Gabcke, in 1896, although he failed to demonstrate the presence of Hassall's corpuscles.

In 1892, Schneider reported a case of *fibrosarcoma* of the thymus without, however, having absolute proof that the tumor was of thymic origin as no Hassall's corpuscles were reported. The cells were of the round cell type and the connective tissue was quite marked.

In 1898, Ertmann reported a *large cell sarcoma* of the thymus in a man forty years old. The tumor filled the anterior mediastinum and extended as far upward as the thyroid. No Hassall's corpuscles were found.

In 1903, Torri reported a case of *myosarcoma* of the thymus in a woman fifty-six years old. The tumor was rather firm, lobulated, occupying the anterior mediastinum. The microscopical examination showed the tumor to be composed of lymphoid cells, small, round-cell sarcoma, and large cells resembling fibromuscular cells. Furthermore, numerous Hassall's corpuscles were present. The origin of these fibromuscular cells is rather difficult to understand unless they should be related to the myoid cells which may be encountered in the thymus.

Carcinomatous Thymoma.—This type appears to be formed of cylindrical or cubical epithelium lying in dense connective tissue. In some cases the cells are chiefly cubical and arrange themselves in concentric layers whose structure resembles the Hassall's corpuscles. In some instances they show typical alveoli, hence, the name, too, of alveolar carcinoma.

Carcinoma of the thymus may be classified as, 1st, epithelioma of the Malpighian type; 2nd, medullary carcinoma. This classification is made according to the predominating type of cells present in the tumor.

In the epithelioma the cells composing the growth are generally somewhat large and resemble those seen in the Malpighian layer or stratum mucosum of the skin. Letulle mentions mucoid degeneration of the cells.

The carcinomatous thymoma takes its origin, most likely, from embryonic residues of the thymopharyngeal duct, or from the reticular cells, or from the Hassall's corpuscles.

Mixed Malignant Thymomata.—Not so uncommonly both types of tumors are mixed together, as in the thyroid. They present histologically the characteristics of sarcoma and carcinoma combined.

Clinical Syndromes (Status Thymicus, etc.). . . . . .

. . . . . *George H. Hoxie*

Historical—Present Status of the Thymus Problem—Clinical Aspects of the Thymus Problem—Thymic Asthma—Mors Thymica—Status Thymicolymphaticus—Etiologic Considerations—Subjective Symptoms—Timme's Multiglandular Syndrome—The Thymus in Exophthalmic Goiter—Myasthenia Gravis—Thymus in Tetany—Thymus in Prostatitis—Clinical Symptomatology of Thymic Hyperplasia—Diagnosis of Thymic Enlargement—Treatment of Enlarged Thymus.

Clinical Syndromes (Status Thymicus, etc.)

GEORGE H. HOXIE

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Historical

The thymus has been the subject of much controversy for nearly three hundred years; and in spite of the great amount of work devoted to it no unity of opinion is as yet apparent. It was hoped that animal experimentation would furnish the key to the puzzling clinical reports, but thus far no series has been accepted as final.

The clinical interest in the subject centered first upon the observations of thymic asthma and thymic death which had been accumulating from the days of Plater (1614), until Paltauf's syndrome of status thymicolymphaticus widened the clinical field, and caused observers to study the characteristics of that class of patients from which the victims of thymic asthma and thymic deaths were drawn.

Of late years, clinical interest in the thymus has been further increased by the discovery (Weigert, 1901) that thymic tumors were present in a large proportion of patients dying of myasthenia gravis. Even the lymphorrhages have been called thymic lymphocytes.

Still more interest has been aroused by finding that in 60 per cent to 95 per cent of the patients suffering from Graves' disease there was an enlarged thymus; and that in such cases thyroidectomy without thymectomy (or the equivalent radium or X-ray treatment) failed to relieve the symptoms.

Present Status of the Thymus Problem

The status of affairs to-day is, then, that an increasing number of observations show that the thymus is involved in these disease syndromes. Whether its relation to them is at all causal remains to be proven.

The weight of evidence would seem to indicate that thymic hypertrophy and hyperplasia are a response to constitutional conditions in which the thyroid proves itself failing or inadequate. That is, it is a phenomenon

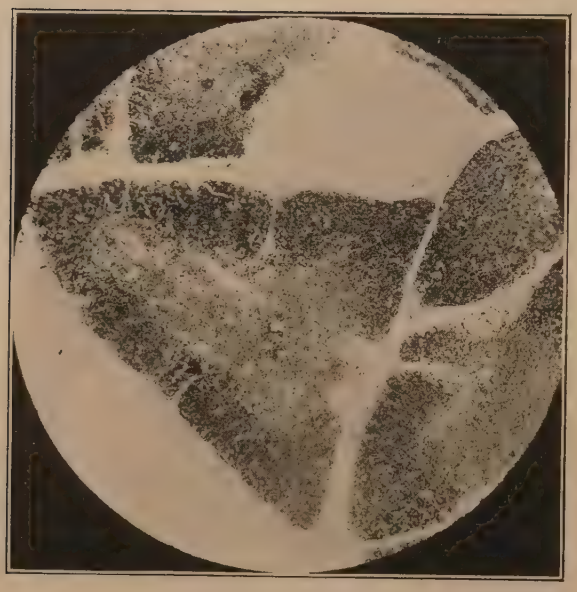

Fig. 1.—Thymus of an infant eleven hours old.

Fig. 2.—Thymus of an infant three months old.

secondary to conditions elsewhere, and like fever should lead the observer to seek out the primary cause. Certain it is that the problem is worthy of study, and that it will be solved only by continued interest and the accumulation of exact observations.

It would seem that secondary hyperplasias of the thymus are accompanied by noticeable myasthenia, even in the case of Graves' disease. And in those cases one finds a predominance of the epithelial elements of the gland. On the other hand, the swelling of the gland, due to lymphocytic

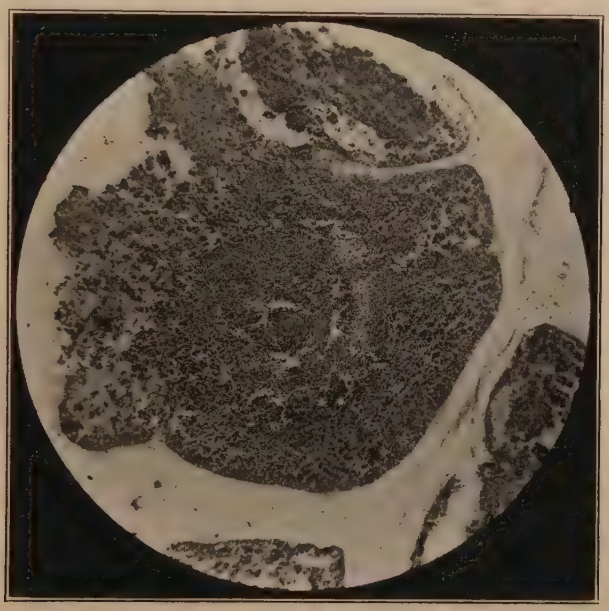

Fig. 3. Thymus in a child four years old dead with mors thymica (Dr. Addison Lea).

invasion, seems connected with a toxic influence on the body,—whether in Sajous' sense of nuclein metabolism, or in Symmers' sense of anaphylaxis remains unsettled.

The accompanying figures (Nos. 1-5) illustrate the normal thymus at birth and at three months, the hyperplastic thymus at four years, the participation of the thymus in a septicemia at twenty-three, and the type of thymus found at operation in a case of myasthenia.

Clinical Aspects of the Thymus Problem

In its clinical aspects the thymus problem presents a number of interesting phases. These will first be taken up under the captions: Thymic Asthma, Mors Thymica, Status Thymicolymphaticus, Timme's Multi-

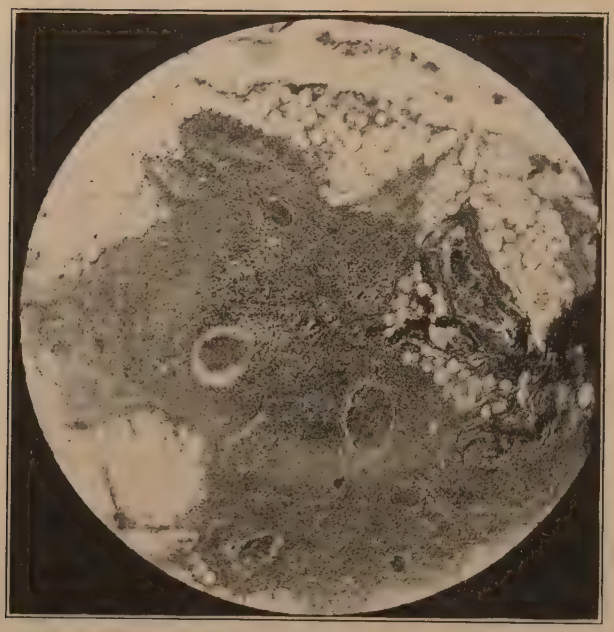

Fig. 4.—Thymus in case of septic abortion, age 23.

Fig. 5.—Thymus tissue removed at operation in a young adult.

glandular Syndrome, the Thymus in Exophthalmic Goiter, Myasthenia Gravis, the Thymus in Tetany and the Thymus in Prostatitis. This presentation will be followed by sections on clinical symptomatology, diagnosis and treatment.

Thymic Asthma

The term thymic asthma originated with Kopp in 1829. The existence of the syndrome was denied by Friedleben in 1858. But nevertheless, a sufficient number of cases of respiratory stridor occur from year to year to keep the concept before the eyes of pediatrists and family doctors.

In the recent literature the most convincing report is that of Chevalier Jackson (*a*). The patient had been observed by several physicians. It

Fig. 6. Infant soon after birth, before radium treatment (Brayton and Heublein).

could not be, therefore, an error in observation. The condition had existed six weeks. At the operation, "On passing one of my bronchoscopes I discovered a scabbard trachea with a chink not over 2 mm. on inspiration and 1 mm. on expiration, the obstruction extending from the second to the fourth rib. The tracheal mucosa was collapsed from before backward almost into contact." Temporary relief was obtained by inserting a tracheal cannula, and permanent relief by thymectomy.

Another observation is that of Pitfield, wherein the use of massive doses of the X-ray brought relief.

Still another report of a careful observation is that of Brayton and Heublein who report seeing an inward bulging to the extent of half the lumen at a point two inches below the vocal cords.

Parker's case is also very instructive, both on account of the accuracy of observation and the successful therapy.

Olivier's reports are fairly conclusive evidence as to the mechanical effects of the hyperplastic thymus, and should leave no one in doubt as to the possibility of the occurrence.

The accompanying illustrations (Figs. 6-7-8) show the X-ray pictures in the following case reported by Brayton and Heublein: A male infant, twelve pounds in weight, was seen one hour after birth. The labor had been easy, but with the first cry the obstetrician had noticed that the child's breathing was decidedly abnormal. The patient presented the

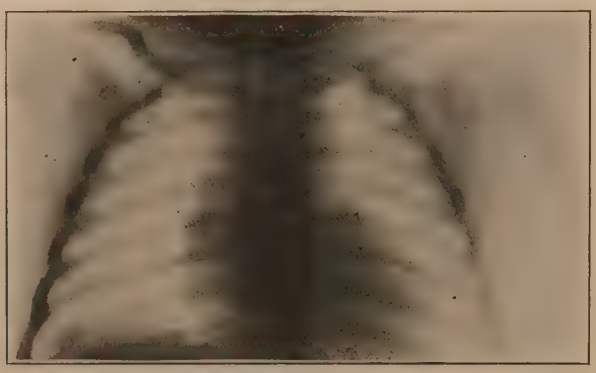

Fig. 7.—Same, one week later.

most unusual appearance; the skin, lips, and nails were intensely cyanotic, and the inspiratory stridor was distinctly audible in the adjoining room, while the epigrastric retraction was equal to that accompanying the severest form of laryngeal diphtheria. Percussion and X-ray both detected the presence of a thymus filling nearly one-half the chest cavity,

Fig. 8.—Same, ten weeks later.

while inspection, palpation, and X-ray all revealed the presence of an enormous thyroid occupying the entire front of the neck as far back as the lobes of the ears. Radium was applied and within forty-eight hours the baby showed decided improvement which continued until, at the end of a week, he was nearly normal in appearance. It was interesting to note that

the enlargement of the thyroid disappeared coincidently with the shrinkage of the thymus. X-ray plates two and ten weeks after treatment showed a normal thymic outline. The child was still perfectly well after fifteen months after discharge from the Hartford Hospital.

Since the cause, if mechanical, must cease to operate when the chest expands, thymic asthma could be a disease only of infancy. This agrees with clinical observation.

Our conclusion must be then that the hyperplastic thymus may cause tracheostenosis, and that this does occur occasionally, especially after crying or other disturbance that leads to an engorgement of the mediastinal tissues.

The presence, therefore, of a hyperplastic thymus should be looked for whenever an infant is being examined. In the infant this can be fairly accurately done by finger percussion, and all doubt can be settled by using the X-ray. (The technic of this procedure will be discussed below.)

In the presence of such a hyperplastic thymus, drastic medical and surgical procedures should be undertaken with great caution,—and if practicable, only after the use of therapeutic doses of the X-ray or radium.

Mors Thymica

It was the occurrence of sudden death in previously apparently healthy children that first called attention to thymic hyperplasia. Thus, Grawitz (1888) could find no explanation other than the pressure of the thymus on the trachea in two cases observed by him. But in other cases the thymus did not seem large enough to exert a deleterious pressure. Consequently there have arisen two theories in explanation of thymic deaths: the one mechanical; and the other chemical (or anaphylactic).

The adherents of the mechanical theory point to many clinical observations of very evident asphyxiation. Such an observation is that of Chevalier Jackson, quoted in a previous paragraph. Another is that of Douglass, who writes the following vivid description:

". . . the dyspnea was much worse, stridor increased, cyanosis rapidly increasing, face becoming anxious, and all features of the case presenting a grave aspect. We decided that tracheotomy offered the only possible chance of relief. . . . A few whiffs of chloroform were given, and as the initial incision was finished, the chloroform withdrawn. The subcutaneous fat was abundant. There was no oozing of blood following the cut. Her heart was racing, a pulse count impossible. As soon as the cut was extended through the fat the thymus filled the wound completely, and extended as far above and below as could be felt. It was deep purple-red in color, covered with small hematomata from about 2 mm. to 6 or 8 mm.

in diameter. Its blood vessels were large and tortuous. It was distinctly lobulated. It filled the space in front of the trachea completely, and was so intimately adherent to the structures below that it could not be drawn aside to expose the trachea. The only way the trachea could be reached was by cutting through the gland substance. This was attempted, but on trying to sponge away the blood, it would well up and fill the wound, rendering a clear operative field impossible. This so delayed the operation that we could not get an opening into the trachea before death ended the scene."

On the other hand, we find such reports as this, from Thursfield (*a*): "A boy aged thirteen months suddenly sat up, his eyes became fixed, he ceased to breathe, became very slightly blue, and then quite white, and fell back dead. The whole series of events occupied less than thirty seconds."

Another case, this one from Falls, will show how very puzzling is the problem. "The baby breathed without difficulty until two hours after birth, when the respiration became difficult and the child cyanotic. This condition lasted for two hours when the cyanosis deepened, respiration became more difficult and the child died without convulsions. Before and after birth the heart sounds were normal; just before death the pulse went down to 30 per minute. At autopsy the skin of the head, neck, arms and thorax was red and congested. The head showed no signs of trauma. The pericardial sac contained a large amount of serosanguineous fluid, and the left lung was compressed and pushed to one side by a large thymus 4 cm. broad at its widest part, and 5.5 cm. long. Crossing the upper portion of the thymus, from left to right at the upper border of the clavicle to the level of the lower border of the first rib, was the left innominate vein. This had compressed the thymus and lay in a groove on its surface. A branch of this vein left the thymus at about the midline of the body. There was no evidence of thrombosis in the thymic veins, the left innominate or superior vena cava. There was edema of the posterior portion of the lung, more marked on the left side, and there were small hemorrhages on the substance of the kidneys. Histological examination of the hypophysis, thymus, thyroid, adrenal and spleen revealed no abnormalities. The trachea was opened just above the upper edge of the main portion of the gland. There was evidence of compression of the trachea by the main body of the thymus, as shown by the difficulty in passing a probe downward from the opening."

Hammar is quoted by Gordon as showing that the mechanical cause was not operative in cases of thymic death. Thus he examined sixteen cases and found the size and histology no different from that in an equal number dead from other causes. Against the validity of Hammar's reasoning, Jackson points out that the condition post mortem does not parallel the condition in vivo, in that the congestion is absent, and the tissues (in-

cluding the trachea) have fallen back into their normal relations and shapes.

We are thus left with the realization that in a certain number of cases this sudden death of infants may be due to asphyxiation, but that in other cases we must look to other causes. Inasmuch as these sudden deaths occur chiefly among the victims of the status lymphaticus, we will discuss the possible causes under that head.

Status Thymicolymphaticus

Many children enter upon life with such abnormal constitutions that they do not respond to the foods ingested, or to the stimuli of the outside world in the same way as do the great majority. Writers have attempted to classify these abnormalities and analyze their causative factors. Thus, some have revived the terms found in humoral pathology, and speak of diatheses. Others see in the eczematous skin and deranged digestion evidence of the vagotonia of Eppinger and Hess. Others, like Haeckel, speak of *émotivité* and the *nevrose d'angoisse*. But more generally, such abnormalities are being traced to dysfunction of the endocrin glands. This view seems to us thoroughly justified, because the endocrin glands seem always involved in these cases and also because it affords something tangible and adequate for study and classification. Considered from the latter standpoint, the best defined group of such disorders is that designated by Paltauf (in 1889) as the status thymicolymphaticus, thus implicating the thymus in its causation.

The most thorough studies of this syndrome seem to have been made at the Bellevue Hospital (New York); Symmers has presented an exhaustive report of the findings among the first 4000 postmortem examinations in that institution. He defines the condition thus: ". . . a combination of hereditary constitutional anomalies, entering into which are certain peculiarities of configuration, with preservation or even hyperplasia of the thymus gland at an age when involution is to be expected, hyperplasia of the lymphoid cells in the lymphnodes, spleen, intestine, and elsewhere; hypoplasia of the cardiovascular system, developmental deficiencies in the genitalia, and, incidentally, visceral defects of uncertain occurrence and irregular distribution."

Haven Emerson, of the same institution, lays down the diagnostic criteria thus: "For the present it seems to me that a diagnosis of status lymphaticus is justified when we find, in the case of a man, a decided scantiness of the hair on chin and upper lip, scanty axillary and sternal hair, scanty or feminine distribution of pubic hair; the slender thorax; the rounded contour of upper arms and thighs, with an arching of the latter; hypoplastic external genitals, particularly if associated with cryptor-

chismus; and a delicate velvety skin. The diagnosis is further confirmed if we find hyperplasia of the lymph tissue of nose, throat and tongue and an increase in the palpable cervical and axillary lymph-nodes.

"For the identification of status lymphaticus among women, we rely on the peculiar character of the skin of the body and extremities, the scantiness of the axillary hair pad, the scantiness of the pubic and perineal hair, hypoplasia of the genital apparatus, and particularly slender thorax and extremities. Some women of decided status conformity have a marked growth of hair on the face and upper lip."

Symmers gives the prognosis thus, "The condition is sometimes terminated by death, usually in children, but occasionally in young adults." He thus links up the syndrome with mors thymica.

He finds it a dangerous condition because (1) "it is attended by instability of the lymphoid tissues, providing a mechanism which, when it is once set in motion, is capable of so sensitizing the body as to produce anaphylactic phenomena varying in intensity from simple urticarial rashes to convulsive seizures and sudden death. The same irritability of the lymphoid tissue is apparently responsible for lowering the threshold of infection, particularly of those infections which gain entrance through the pharyngeal and faucial tonsils and the intestinal tract."

(2) "It is a menace, because it is attended by defective development of the muscular coat of the arteries, thus rendering them incapable of withstanding changes in blood-pressure which in other circumstances are lightly borne."

In Bellevue Hospital 249 examples were found in the 4000 autopsies previously mentioned. Of the subjects, 212 were males and 37 females. Their ages were:

Under 1 year	22
1 to 10 years	10
11 to 20 years	20
21 to 30 years	62
31 to 40 years	57
41 to 50 years	41
51 to 60 years	19
Over 60 years	11

This should not be taken as standard for the occurrence of this syndrome among the populace at large because a public hospital in the congested part of a large city is not so apt to have the same proportion of babies from all classes, and of young females as would represent the normal run of our American population. On the other hand, the males afflicted with status lymphaticus would tend to failure in early adult life and thus reach just such a hospital in relatively large numbers.

Now taking the 116 cases of well developed status, Symmers found the thymus hyperplastic in every instance. The weight was recorded in sixty-six cases. The youngest was an infant eight hours old, whose thymus weighed 70 grams, and in whom death occurred suddenly. The oldest was an acromegalic individual aged thirty-eight years, in whom the thymus also weighed 70 grams and in whom death was due to an intercurrent infection. The average weight of the thymus was

Under 1 year	25	grams	13 cases
1 to 5 years	18	grams	14 cases
6 to 10 years	24	grams	5 cases
11 to 15 years	22	grams	5 cases
16 to 20 years	23	grams	9 cases
21 to 30 years	27.8	grams	17 cases
31 to 40 years	33.8	grams	3 cases

The faucial tonsils were hyperplastic in 61 instances (51 per cent), the lingual tonsils in 58 (49 per cent), and the pharyngeal tonsils in 45 (37 per cent). Peyer's patches and the solitary follicles were each hyperplastic in 105 cases (88 per cent). The spleen was small or normal in 68 cases (70 per cent). "In our experience, enlargement of the spleen is not a part of the pathology of status lymphaticus, and should not be taken into clinical account except as it has to do with associated conditions."

The status lymphaticus has become so important that James Ewing (*b*), consulting pathologist of the Surgeon General's office, asked that medical officers of the army note and report the effect of military life on men of this type. As an illustration of such happenings, we may quote from Rice the following case history of a sudden death: "Lieut. C. C. N., age twenty-nine, was and had been in good health when he was given 0.5 c.c. of standard U. S. Army bacteria containing paratyphoid A and B, about 4 p. m., August 18, 1918. The bacterin was given under the subcutaneous tissue of the left arm over the deltoid, and he neither complained nor demonstrated any symptoms of shock, but during dinner he complained of headache and indefinite hot and cold flashes in his lower extremities. Without eating as much as usual he left the table and went to his room, after which he was not seen during the evening. Nothing unusual occurred in his room, but one of the officers thinks that he went to the bathroom and vomited about 11 p. m. The following morning he did not come to breakfast, and some one went to this room at 7:30 a. m., where he was found dead in his bunk. He was lying on his back in a comfortable position, one hand resting on his abdomen, the other at his side, the fingers relaxed. His pupils were equal and normal, neither the tongue nor the lips had been bitten, nor were there any signs of a struggle or of violence about the body. At 4 p. m. I performed an autopsy and found a complete picture of status lymphaticus. There was a small excess of straw colored

fluid in the pericardium. The right heart showed some dilatation and the musculature was flabby, but there was no hypertrophy. All valves were normal except the aortic and they showed some thickening of no importance. The aorta was strikingly small and measured 6 cm. in circumference. There were several atheromatous patches in the arch, and one of them encircled the right coronary. But the coronary was patent throughout its length and showed no evidence of sclerosis; nor was there any sign of an embolus. The thymus was large, thickened, and extended down over the right auricle. On cross section it was congested and 'meaty.' Its dimensions were: length 7 cm., width 4.8 cm., with an average thickness of 1 to 1.2 cm. . . . The spleen was twice its normal size, dark red and bloody on section, with prominent follicles. . . . I cut down on the brachials, femorals and carotids. None of them was more than two-thirds normal size, the right brachial being the smallest. And none of them was sclerosed."

As a further indication of the effect of status lymphaticus in military life, we have the report of Davis who examined two groups of soldiers as to the prevalence of the stigmata of status lymphaticus. Among 114 psychoneurotics—men who had been returned from France—he found the status type in 23.68 per cent. Among 119 cases of battle casualties—men who nevertheless had not developed psychoneuroses—he found the status in 12.60 per cent. This report would tend to emphasize the lack of stamina among the victims of the status, both in the nervous and mental realms, as well as in the purely physical. It would also emphasize the need of watching out for this condition whenever we examine men for military duty, or for other arduous employment.

Etiologic Considerations.—It is in explanation of the sudden deaths of these folk that the students of the thymus have been most at variance. To say that the hyperplasia of the thymus is compensatory simply dodges the issue. We do not know what it is that is lacking.

Tracy speaks of a hormone secreted by the thymus. Noël Paton believes that the condition is one of endocrin imbalance, in which disastrous results are precipitated by apparently trivial traumata. McNeil holds to the theory of anaphylaxis. Wooley seems to consider the thymus responsible for the untoward results of status lymphaticus but just what rôle is played by the thymus in this connection is still not clear. Thus, Sajous seems to consider it connected with the phosphorus metabolism. Others believe it concerned with the nucleoproteids,—especially, with those found in the lymphocytic nuclei.

The most adequate current statement of the case of the adherents of the sensitization theory, is that of Symmers:

"Sudden death in subjects of status lymphaticus has often been ascribed to pressure of the enlarged thymus upon the trachea. At Belle-

vue Hospital, we have not been able to implicate the thymus as a mechanical factor in the production of death, the anatomical signs of tracheal compression and death from suffocation never having been found, though sought.

". . . It is more probable that death is of the nature of an anaphylactic reaction, sensitization being expressed in structural terms of the necrotic germinal follicles, and chemically, by the release of nucleoproteids which, though not strictly foreign, are none the less pathological; and are comparable in a toxicological sense to alien products. Previous to the expiration of the so-called anaphylactic incubation period, the lymph nodes are again subjected to the action of destructive substances which serve to bring about still further disintegration of germinal nuclei, thus providing the requisite quantity of specific proteid to complete the anaphylactic cycle. The destructive substances may be introduced in the form of antitoxins hypodermically administered, or as vaccines applied by scarification or otherwise, or as substances which have escaped destruction or modification by the hyperplastic lymphoid follicles in the intestinal tract, or which have been manufactured in the processes of shock induced by even such simple procedures as the prick of a needle, sudden immersion in cold water and similar events."

Among foreign writers there is also this same sense of the inadequacy of our present knowledge of the subject. For example, Friedjung is decidedly of the opinion that the term status lymphaticus is justified as affording a serviceable grouping of allied happenings. But he does not find in the German literature any adequate explanation for all the clinical phenomena. He reviews the views of Escherich, Thiemich, Rosle, Wiesel and Bartel, and contrasts them with Czerny's desire to throw aside the whole conception and think only in terms of an equally vague "neuropathological constitution."

The French are inclined also to speak of diathesis, rather than of status lymphaticus. But Olivier and Veau's writings do add material strength to the theory that the thymus has a causal relation to the general condition.

If the condition were simply constitutional, heredity and environment should play an important rôle. But only occasionally has the occurrence of status lymphaticus in families been noted. Of these, one of the most complete of the recent reports is that of Bierring, Goodrich and Glomset, treating of four cases in one family. All died suddenly and within a short period; the authors were able to make thorough postmortem studies. They are inclined to believe that the histologic conditions found were the general reaction of the tissues to some chronic irritation, and thus neither inherited, nor congenital nor even diathetic.

That status lymphaticus has nothing to do with hereditary syphilis is shown by the distinctive changes found in the thymus when that organ is

affected. Thus, we have the Dubois abscess (Oliver), or the diffuse small cell infiltration of Schlesinger, or the gummata (which may break down into cysts). In no cases thus far reported has there been a status lymphaticus connected with such findings.

Subjective Symptoms.—Finally, as to the effect of the status thymicus on the patient, the following statement from Houghton (*a*) is pertinent: "It is evident from my cases that this myasthenia is a most characteristic symptom of status thymicus. The typical history as given by a patient recently is, 'I awake in the morning feeling splendidly, though the night's sleep may have been poor. My first thought is as to how much I can accomplish during the day. After a good breakfast, I take a walk as I have been advised to do, and before I have gone two blocks I begin to feel tired. If I continue, I am compelled to sit down and rest before a half mile is covered, and for the rest of the day my strength is gone.'"

It is well to contrast this with the story of the typical neurasthenic, whose worst time is in the morning and whose only joy in living comes later in the day. Much confusion and also much unhappiness has arisen from the failure to make the differential diagnosis between these two fundamentally different conditions. This consideration emphasizes the necessity of making a general physical examination of all patients, even though they seem to present only functional and neurotic symptoms. Even in the adult, the status thymicolymphaticus calls for protective hygiene and extra stimulation.

Hygiene.—In the way of *hygiene,* the protection from overstrain, both physical and mental, is of primary importance. Growing children must be protected from the grind of the regular school curriculum. They must have shorter hours and more frequent vacations than the average child. In particular, it is wise to send them every year to the mountains for the effect of the altitude in expanding their chests and strengthening their weak arterial systems. In my practice I have seen children practically transformed by spending eight to twelve weeks each year at an altitude of six thousand feet or more. This should be continued until the thymic involution at puberty aids in the reduction of the organ to a size relatively smaller than its mediastinal container.

Even after puberty, it is important that these patients should not be allowed to dissipate their strength either in school or social excesses. If they engage in business or professional life, they must be taught to respect the signs of overstrain and curb their ambition to fit their strength.

In the way of *stimulation* I have found nothing quite as effective as arsenic, especially when it is administered intramuscularly in the form of sodium cacodylate, or arsacetin.

Timme's Multiglandular Syndrome

Timme has postulated a multiglandular syndrome, which he has been able to trace through from childhood to the third decennium. This syndrome should be differentiated from status lymphaticus, with which it is liable to be confused. In it the rôle of the thymus seems to be compensatory rather than primary. The syndrome is discussed in detail in the chapter on Multiglandular Syndromes.

Thus far the literature shows no comments on the described syndrome. Its merit is the attempt to work out the sequence of endocrin interactions in a given type of cases. It is quite probable that several such diagrams of endocrin imbalance will be drawn before we succeed in grouping even the majority of these disorders.

The Thymus in Exophthalmic Goiter

For a long time Graves' or Basedow's disease was considered synonymous with hyperthyroidism. But now it is recognized that many cases are examples of relative hypothyroidism. With this recognition has come the discovery that the thymus is often involved in the syndrome and that it seems to have an effect on the symptomatology. Thus Garré and Capelle found an enlarged thymus in 95 per cent of the fatal cases of exophthalmic goiter studied by them. Eddy collected reports on 240 cases and found that the thymus was persistent or enlarged in 201 or 83.75 per cent. Others estimate the proportion at 60 per cent. Hart (*f*) even believed that there is a purely thymogenetic form of the disease. Halsted and others have attempted to classify the symptoms into two groups according to the predominance of the vagotonic or thyroid elements, or of the sympathetic or thymus elements. This has proven difficult to carry through in the present state of our knowledge. But many students of the thymus see in the myasthenia, sometimes accompanying Graves' disease, the influence of the reactivated thymus.

On the other hand, such experienced observers as the members of the Mayo clinic believe that if the thymus participates at all in the symptomatology of exophthalmic goiter, its rôle is a negligible one. These differences in opinion make necessary a critical study of every case of Graves' disease until the contradictions presented in these divergent views have been eliminated.

In the first place, it is necessary to define the disease anew. And such a definition should be expressed in terms of both pathological physiology and pathological anatomy. Toward this end Plummer's contributions are very helpful, for he limits the term, exophthalmic goiter, to those cases which show, not only the traditional triad of exophthalmos, tremor, and

tachycardia, but also an increased metabolic rate as shown by the calorimeter, and which present also a diffuse enlargement of the thyroid gland. Cases of adenomata with hyperthyroidism belong, in his judgment, to another syndrome and offer a different prognosis.

Further studies in different localities of the rate of basal metabolism, of the sugar tolerance, of the adrenalin sensitization, will be needed before we can safely state that the thymus and other glands do not play a rôle in exophthalmic goiter, and do not need attention when treating the disease. Certain it is that there is something besides pure hyperthyroidism in

Fig. 9. Shadow in case of exophthalmic goitre where a thyroidectomy gave only partial relief (age 30).

exophthalmic goiter. This something is being interpreted by many observers as the participation of the sympathetic nervous system in the syndrome.

If now we accept myasthenia, breathlessness, low blood pressure, dry skin, relaxed intestinal tone, etc., as the common symptoms attending thymic hyperplasia, we must admit that they are the same as those presented by sympatheticotonia.

Naturally then, we would conclude that thymic hyperplasia is an accompaniment of sympathetic overbalance, and that, therefore, the hyperplasia of the thymus in exophthalmic goiter is simply one evidence of the reaction of the vegetative nervous system, of exhaustion of the parasympathetic [1] system due to continued overstimulation.

[1] Much confusion in terminology could well be avoided by the use of Langley's original terms *sympathetic* and *parasympathetic* as subdivisions of the autonomic nervous system proper.—R. G. H.

If this be accepted as a working hypothesis, separate treatment of the thymic hyperplasia would not be demanded in cases of exophthalmic goiter. But on the contrary, we should expect the sympathetic system to return to normal in all except the worst cases as soon as the parasympathetic system had regained its tone. But in these worst cases—cases in which the thymus has become a positive influence in the bodily economy—the radiologic treatment of the thymus is certainly indicated.

Myasthenia Gravis

Nature of the Disease.—This syndrome was recognized by Erb in 1891, and its definition has been given greater precision by several succeeding writers, e. g., Goldflam, Buzzard, Oppenheim, Weigert, Jolly. At present the widest acceptance is accorded to McCarthy's formulation of the definition: ". . . a disease with fatigue symptoms referable to the muscular system, due to an exhausted condition of the innervation, without definite pathology in the nervous system and with minor changes (lymphocytic infiltration) in the muscles." While the ocular muscles may be the first, or those most prominently involved, it may be limited to the movement of the limbs (Anders-Boston). In the morning, or after a long rest the movement of the affected muscles may be almost normal. But they soon tire. The usual clinical test of the condition is to stimulate the muscles with the faradic current. After a few apparently normal contractions, the muscle ceases entirely to respond (Jolly). This muscular weakness has frequently led observers to classify their cases under the paralyses, and thus to lose sight of their true significance; e. g., Major's case was reported simply as leukemia with paralyses.

Occurrence of Thymic Tumors in Myasthenia Gravis.—In 1901, Weigert reported the finding of a thymic tumor in two cases of myasthenia gravis. Since then many more have been reported. Thus Mandelbaum and Cellar collected reports of eleven thymic lesions in a total of forty-five cases. The study of these tumors had not led to unanimity of opinion until Ewing (*a*) and Bell (*b*) showed that they are essentially derivatives of the embryonic thymic tissue. Ewing, therefore, calls them thymomata. Whether or not the lymphorrhages in the muscles and visceral organs are to be ascribed to an excess of thymus lymphocytes, or whether both have a common origin as a reaction to a diffused toxin remains unsettled.

Illustrative Case.—Jones' case was so well studied that it is worth while to reproduce here the history: "To the best of the patient's knowledge, he was in perfectly good health three years before. About May, 1912, following an exposure to cold while working in water as a ship's carpenter, he noticed within a few days a marked weakness of his neck muscles, and within two weeks he had developed a condition similar to the

one from which he suffered when examined. The symptoms came on rather slowly, and were associated with slight pain and soreness in the muscles of the shoulder and back of the neck, followed by general muscular weakness, and particularly by inability to close the mouth, to swallow solid foods, or to drink liquids. This condition progressed until the patient became much emaciated, and was almost unable to take nourishment at all. This illness lasted a few weeks, when he began to improve and recovered his strength. Within six months after the onset of his primary symptoms, he claimed that he was perfectly well, and during the interim he did not recall that he had felt any weakness of muscles or any inability to swallow or to speak. Up to February, 1915, he was in his usual good health, and was able to attend to his work. During this month, without apparent cause, unless it was a slight cold, as he expressed it, following exposure, the above named symptoms began to return. There was pain in the jaw, but not of severe type. Gradually the muscles of the neck and throat became weak, and he was unable to move his jaw, or to swallow or drink with his usual ease. At the time of his admission into the hospital, in November, 1915, he had a slight ptosis of the right eyelid. The weakness that he complained of was most marked in his neck muscles, but the entire musculature was more or less involved, and during the time that he was under observation he was unable to walk, to make any marked exertion, or to eat a full meal. After a good night's rest the patient was much better, but as the day went on his weakness became more marked. At the beginning of a meal, swallowing and other movements of the jaw were comparatively free; but after a few moments the muscles tired, and he was unable to continue. It was difficult for him to blow his nose, and he was obliged to have his mouth closed and his chin held in position until he could force air through the nostrils. After talking for a few moments he was obliged to hold his lower jaw with the aid of his hand. Aside from this general weakness, and particularly of the muscles of the neck and jaw, and his inability to finish his meal, the patient felt fairly comfortable. On December 10, 1915, he complained in the afternoon of a general fullness of the chest, with evident dyspnea. A hypodermic of 1-200 grain of atropin was given, with the hope that it might relieve his distress. Ten minutes later he suddenly died."

The postmortem examination was made by Bell, whose previous work on the thymus made him particularly well qualified for the task. The following is quoted from his report: "The tumor tissue consists of cells with large vesicular nuclei and abundant light staining cytoplasm, fused together to form a syncytium. Throughout the syncytium are numerous spaces of variable shape and size, containing small lymphocytes. In some areas the lymphoid cells predominate, in other areas the epithelial cells. To those familiar with the histogenesis of the thymus it will be clear that this tissue corresponds closely to the structure of the embryonic thymus at

the stage when the epithelial organ is being transformed into a lymphoid organ. The cells with large clear nuclei are thymic epithelial cells. . . . There is no true differentiation into cortex and medulla in any part of the tumor examined; but some areas contain many more lymphocytes than other portions. It is to be remembered that the entire reticulum of the thymus is of epithelial origin, and that the cortex normally contains a great many more lymphocytes than the medulla—the latter retaining somewhat of an epithelial appearance in the fully formed gland.

"No corpuscles of Hassall are to be seen. These structures do not appear in the development of the thymus until the medulla has become well defined, and since the tumor tissue has not yet attained that stage of differentiation one would not expect to find them. However, there can be no doubt that the tumor is composed of young thymic tissue, even though no corpuscles are present."

Subacute and Arrested Cases.—As the syndrome is becoming better known, more cases are being recognized; and there are appearing case reports of all degrees of *formes frustes* as well as reports of apparent recovery or at least of remission. Rosenbeck, for example, reports two such cases. Thus there is ground for hope that the accumulation of greater material will enable us to understand the disease better, and ascertain the rôle of the thymus therein.

Treatment.—One cannot help feeling that the treatment of the thymus in this disease is justified,—and that the type of treatment should be that of exposure to the radium or the X-ray, on the theory that thymic overactivity is responsible for many of the symptoms.

Thymus in Tetany

Latterly, the laboratory workers have implicated the thymus in the tetany which appears occasionally among experimental animals. Very little on the point has appeared in the literature from the clinicians. In my own experience, there is only one case that suggests the condition. This was that of a physician who had a combination of prostatitis and submanubrial dullness ascribed to thymic hyperplasia. His myasthenia and "nervousness" had reached a point where it was necessary for him to give up his practice. But the discovery of the real nature of his ailment, and massage of the prostate led to immediate relief and the resumption of his work.

He had two tetanic seizures while under observation, the second one due directly to the milking of the prostate and vesicles. It was accompanied by greatly increased temperature. It is interesting to note that the chest condition cleared up parallel with the prostatitis, thus suggesting that the submanubrial dullness was secondary to the pelvic trouble.

Thymus in Prostatitis

In this connection I should like to call attention to the consistently low blood pressures accompanying this syndrome of inflamed prostate and submanubrial dullness. In apparently robust men the blood pressure will rarely exceed 100 mm. That it is not constitutional is shown by the fact that as soon as the absorption from the prostate ceases, the blood pressure rises to normal levels, and the substernal dullness disappears.

Clinical Symptomatology of Thymic Hyperplasia

In the infant the symptoms of thymic hyperplasia are those due to its size. But in the adult we find another group of symptoms, mentioned briefly in a previous paragraph,—apparently accompaniments of thymic hyperplasia but explicable as being due to the preponderance of the sympathetic nervous system and the related chromaffin rests. The symptoms are asthenia, dryness of skin and sluggishness of all vegetative functions. Thus we find the patients complaining of the difficulty in obtaining adequate breath. They sit and yawn even while attempting to express their complaints. The long sighing breath, usually not oftener than one in six or seven, is more frequent and distressing. Constipation, of the atonic type, also draws attention to the sympatheticotonia. The inability of the patients to administer their business efficiently, or to carry out effectively their work or play, should lead one to suspect this type of disorder.

The differentiation from neurasthenia should not be difficult, because in the latter we find either psychic or vagotonic influences (and symptoms) predominating. This differentiation was noted in our discussion of myasthenia.

In other words, we may expect in the adult some symptoms due to the weakness of the thyroid and its synergists, and other symptoms due to the size and (possible) secretions of the thymus. Thus the lack of energy may be due to the hypothyroidism,—but the sensations of smothering and breathlessness are probably the result of thymic hyperplasia. The blood picture should show a relative increase of the mononuclear elements. But this finding is common to many asthenic conditions and hence is not pathognomonic. No uniform condition of acidosis has been reported. The Goetsch test is usually positive in this condition because of the sensitiveness of the sympathetic system. But the blood pressure is uniformly low, the usual finding being diastolic 60-70 and the systolic 90-100.

Diagnosis of Thymic Enlargement

Lerch was the first to insist on the possibility of diagnosing thymic hyperplasia in the adult by percussion; and it seems to be generally conceded that in pronounced cases every well trained diagnostician ought to be able to note the abnormal areas of dullness. Boggs even went so far as to believe it possible to secure a difference in note between the prone

Fig. 10.—Shadows in the right anterior oblique position.

and the upright positions. But his claim has not been generally substantiated. The type of percussion employed is the very light or threshold percussion, in order to avoid the resonance of the lung tissue.

The finding of submanubrial dullness (i. e., the note over the manubrium duller than that over the corpus sterni and extending out to one or both sides,—but typically to the left) should put one on guard as to the possibility of there being some thymic hyperplasia. The checks are: (1) The whispered voice, heard posteriorly below the seventh cervical vertebra

(d'Espine's sign), points to the mediastinal or bronchial lymph glands as the source of the dullness. (2) The broadening of the aorta (dilatation) usually betrays itself by a band of dullness from the lower manubrium down through the sternum. (3) Thrill and pulsation also point to a vascular origin. (4) The submanubrial dullness should persist in both the horizontal and vertical postures, because the aortic arch may be mobile enough to give different percussion notes in the different postures.

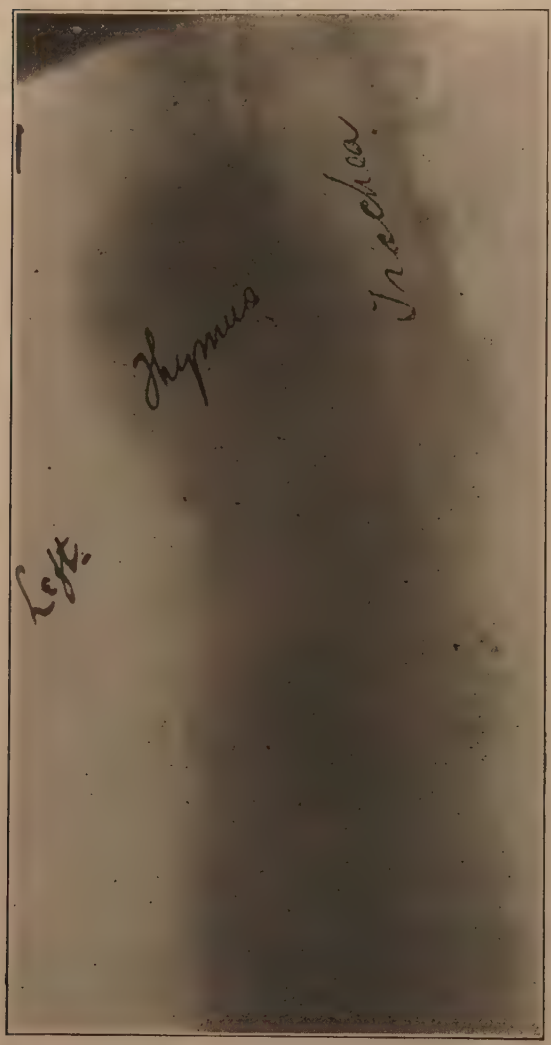

Fig. 11.—Deviation of the trachea in thymic hyperplasia.

If none of these differential signs is present, one should then proceed to use the fluoroscope. The patient should be viewed first in the antero-posterior position. If the presence of an increased shadow be verified, then it should be examined for movement when the patient swallows (thyroid), and for pulsation (aorta or aneurism). Now, by turning the patient and viewing the chest in the right oblique (50 degrees) position of Vaquez and Bordet, one can determine if the shadow fills the clear space between the spine and the vessels. In this case the shadow is due to lymph glands and not the thymus.

The accompanying cut (Fig. 10) shows a skiagram taken in the right oblique position, showing the thymic shadow in the retromanubrial space, in an adult.

Another check is to note if the trachea has been pushed aside by the thymic mass, as in Fig. 11.

For the determination of the presence of an enlarged thymus in chil-

dren, the diagnosis by palpation and percussion is easier; but the confirmation by X-ray should be obtained whenever possible.

For the X-ray technic, I cannot do better than quote Lange: "In most cases a direct diagnosis can be made from a good röntgenogram. The X-ray shadow of enlarged thymus is a wide median one. In some cases the thymus shadow continues directly upward from the heart; in others the thymus shadow appears like a broad cap superimposed on the shadow of the heart and great vessels. But a broadening of the median shadow above the heart is not always due to an enlarged thymus. Benjamin and Goett, in a careful study of the interpretation of the radiograms of the chest in the infant, point out that a broadening of the shadow to the right

Fig. 12.—Normal shadows in the infant (Brayton & Heublein).

may often be due to the superior vena cava. The appearance of the superior vena cava is, of course, familiar to every röntgenologist. The younger the child, the more does the upper mediastinal shadow extend to the right. When the veins are distended, as from crying or struggling, this shadow may extend far to the right and may vary from time to time. When, however, the upper mediastinal shadow extends well to the left, the diagnosis of enlarged thymus is certain. False thymus shadows may be produced by asymmetry of the position of the child when the exposure is made. To avoid flopping of the heart and mediastinum to one or the other side, thus giving false shadows, I have lately been placing the child prone, and while an assistant or nurse holds the body and chest symmetrically, an instantaneous exposure is made. In many cases, however, the X-ray will fail to give conclusive evidence as to the presence of an enlarged thymus. This is especially true when the enlargement is chiefly in the anteroposterior diameter and very little in the lateral. Especially, difficulty in demonstrating the thymus is encountered in very young

infants because of the abnormally broad shadow of the upper mediastinum.

"Furthermore, the superior opening of the thorax in a young child measures only 2 cm. in diameter, and it is in this so-called critical space of Grawitz that pressure occurs. A thymus could, therefore, be comparatively small, that is, less than 2 cm. in thickness, and still might compress the trachea, esophagus, blood vessels, etc., which pass through the superior opening of the thorax."

Friedlander also points out the necessity of using a soft tube, of making an exactly symmetrical exposure, and of focusing on the submanubrial space.

Treatment of Enlarged Thymus

If now we assume the position that the hyperplasia of the thymus is secondary or compensatory to other constitutional conditions, our therapy will be directed chiefly towards the condition of the other organs of the body, and attack the thymus only when its size threatens trouble. In children, however, it is this very matter of size that causes much of the trouble. Therefore, with them we seek first of all its reduction.

The thymus seems very sensitive to the X-ray, and, therefore, in cases of hyperplasia exposure to the X-ray or radium is the method of choice.

Cook quotes with approval Lange's conclusions, as follows:

> "1. Röntgen irradiation of the thymus produces artificial involution of the gland.
>
> 2. X-ray therapy is the method of choice in cases of enlarged thymus in children, whether the symptoms be mild or urgent.
>
> 3. Urgent cases should receive repeated massive doses.
>
> 4. Recurrence due to regeneration of the gland is to be watched for and controlled by further treatment.
>
> 5. Children whose physical or mental development is retarded should, if suspicion is directed towards the thymus, receive tentative X-ray treatment, even though a positive diagnosis cannot be established.
>
> 6. X-ray therapy as a precautionary measure, or pre-operative treatment, may enable children of the so-called lymphatic type to withstand intercurrent disease or anesthetics, which would otherwise prove fatal.
>
> 7. Pre-operative exposure of older children and adults, where there is a suspicion of enlarged thymus, might lessen operative mortality.
>
> 8. Routine pre-operative X-ray treatment in cases of hyperthyroidism should be resorted to with a view to lessening operative mortality.

9. X-ray exposure of the thymus gland has been proven harmless, whether in normal or abnormal individuals. A therapeutic test with the X-ray is, therefore, always permissible."

Friedlander, who has reported a series of over a hundred cases in which only four were unsuccessful, also uses Lange's technic and outlines it thus:

"A Coolidge tube, backing up a nine and one-half inch spark, was employed. The rays were filtered through 4 mm. of aluminum and a piece of thick leather. The target skin distance was approximately nine inches. The routine exposure was twenty-five milliampere-minutes. In mild cases a single dose given over the anterior surface of the chest proved sufficient. In more urgent cases fifty milliampere-minutes were administered at the first treatment, twenty-five anteriorly and twenty-five posteriorly. During the treatment the child was kept quiet by four sandbags, one placed across each arm and one across each leg. The interval between treatments was usually one week unless the urgency of the symptoms suggested more frequent application."

Brayton and Heublein have reported a series of thirty-four cases of enlarged thymus treated with *radium,* with a prompt disappearance of all symptoms. Their technic is as follows: "100 milligrams of radium element, still in its 0.3 millimeter silver capsule, is wrapped in sufficient gauze so that when strapped to the chest by a strip of adhesive, it will lie

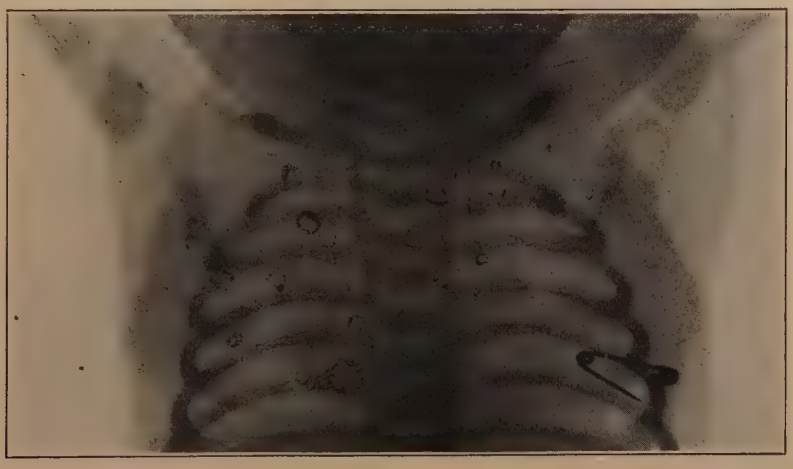

Fig. 13.—Before treatment (Brayton and Heublein).

half an inch from the skin surface. Four marks are made in the form of a rectangle over the thymic area, and the nurse is instructed to allow the package to remain two hours over each mark. This makes a total exposure of 800 milligram-hours. From the moment a diagnosis is made, the child's head should be kept in a flexed position, thus lessening the severity of the asthma and the possibility of sudden death."

The advantages of radium over X-ray are: "The action is more rapid; with radium one treatment alone suffices to effect a cure." "Radium is portable." . . . "The application is so simple that the dangerous element of fear is eliminated . . . and a highly skilled operator is not needed."

Brayton and Heublein's results are illustrated by the accompanying figures of a case in their series (Case 43), the time interval between the two photographs being one week.

Aside from this, I find that *arsenic* administered in the form of arsacetin, or sodium cacodylate, intramuscularly has seemingly a distinctly good effect on the blood picture, as well as on the general condition of the patient.

Fig. 14.—After treatment with radium (Brayton and Heublein).

The *surgical removal* of the gland may occasionally be necessary, on account of the urgency of the case. The technic and results are perhaps best illustrated by the rehearsal of Parker's case. This was a year old child, suffering from convulsions that appeared to be brought on by crying. During these attacks of crying there was a marked stridor. The diagnosis of increased thymic dullness was confirmed by the X-ray. Parker used ether and removed a portion of the thymus 5 cm. by 3 cm. by 1.5 cm., weighing 9 gm. about one-half hour after removal. The child had only one more convulsion, and that just a few hours after the operation.

"The plan of operation was that of Veau. A median incision 4 to 5 cm. long was made with the lower end just below the upper border of the sternum and extending down to the deep fascia. An incision of the deep cervical fascia exposed the sternohyoid muscles which were separated by incision and dissection. This exposed the pretracheal tissues and in the

lower part of the wound could be seen, rising and falling with each respiration the upper portion of the thymus, resembling very closely in color and structure the omentum seen through a thin hernial sac.

The gland when first seen was inside its capsule which was lifted up and encised. Further resembling the omentum, the gland showed a tendency to herniate through the capsule at each expiration, when it was seized with a forceps and gradually stripped of its investing sheath, until the larger portion was extrathoracic, when it was tied off at its more fixed portion under the sternoclavicular junction, where it is joined by the nutritive branches of the internal mammary artery. The wound was closed with deep sutures of catgut in the cervical structures and skin stitches of horsehair.

"The temperature which was normal before the operation, became 102° F. a few hours afterward, and 105° F. the next two days, when it gradually went down to normal at the end of the week. Two slight convulsions occurred during the week.

"At the end of the week the lower part of the wound was found infected, but it drained well and caused no rise in temperature. The early and rapid rise I believe occurred too soon to be due entirely to infection. The further course was uneventful, no more convulsions. No more stridor. The X-ray showed lessened density in the thymic region."

But even Olivier and Veau (*b*), whose success with thymectomy has been most brilliant, latterly advocate the use of the X-ray by preference.

SECTION IV

The Male Gonads and Their Diseases

Anatomy, Embryology, Comparative Anatomy, and Histology of the Endocrine Components of the Testis . . . . . *E. V. Cowdry*

Anatomy—Embryology—Comparative Anatomy—Histology—Arrangement of Cells—The Nuclei—Mitochondria—Centrosomes—Fat Inclusions—Pigment—Reticular Apparatus—Chromidial Substance—Crystalloid Inclusions—Specific Secretory Substances. [From the Anatomical Laboratory, Peking Union Medical College.]

Anatomy, Embryology, Comparative Anatomy, and Histology of the Endocrine Components of the Testis

E. V. COWDRY

NEW YORK

Anatomy

The interstitial cells are scattered between the seminiferous tubules and are often called the cells of Leydig, after their discoverer. Bearing in mind their possible glandular function, Bouin and Ancel (*g*) have applied to them the term of "Glande interstitielle du testicule."

Interstitial cells are often grouped in a most suggestive way about the blood vessels, as is illustrated in Fig. 1. No unusual relations have been detected with lymphatics or nerve fibers. Assertions to the effect that they are controlled by centers situated in the subthalamic region, or elsewhere, are not very convincing in view of the success of transplants, which would seem to indicate that, for the discharge of their duties, they are not necessarily dependent upon the nervous system.

Embryology

According to Felix the interstitial cells develop very early, in embryos of forty-five millimeters, as a differentiation of indifferent mesodermal genitaloid cells, that is to say, before the formation of definitive germ cells. These early interstitial cells may be identified by their large size and pale nuclei, which are almost devoid of chromatin. After the fifth month they apparently become quiescent, and formation ceases until after puberty, when they appear in great numbers. They then undergo retrogression, only to increase again, but the reason for this later increase is obscure and the observations of it require repetition. Even in extreme

old age these cells, like those of many other endocrine organs, retain embryonic potencies, as is shown by their ability to undergo dedifferentiation and give rise to tumors, as described in dogs by Goodpasture. It seems that the interstitial cells of the ovary are less liable to tumor formation.

Fig. 1. Groups of interstitial cells (i) in human testis closely associated with a blood vessel (b.v.) (magnification 680).

The comparative growth energy of the interstitial cells has not been measured by the inanition method. It would seem, however, that their growth is more vigorous than that of the seminiferous tissue, since they develop and function in cryptorchids.

Comparative Anatomy

Interstitial cells occur in most of the vertebrates which have been examined, with the possible exception of certain birds; but their degree of development is subject to enormous variation in different classes. In hibernating animals, like the woodchuck, they exhibit great cyclical changes in number (Rasmussen (*a*)). During the hibernating period they

are reduced, but when the animals become active again and spermatogenesis begins, they increase enormously.

No attempts have yet been made to check them up in a statistical way with other presumably internal secretory tissues, owing, perhaps, to the extreme difficulty of making quantitative determinations.

Histology

Arrangement of Cells.—In adult human testes the interstitial cells vary considerably in number as between individuals. There is no marked difference between right and left testicles. Interstitial cells occur singly and in groups, which may or may not be related to blood vessels (Fig. 1). Sometimes the cells form acinus-like clusters. They are easily identified and may be distinguished from connective tissue cells by their general appearance, as well as by the fact that they do not stain with vital dyes, like trypan blue (Addison and Thorington).

The Nuclei.—The nuclei of the interstitial cells are usually single and spherical, but double nuclei occasionally do occur. Whether or not the double nuclei result from amitotic division, as has been frequently suggested, cannot yet be answered. The nuclei are poor in chromatin and rarely contain distinct nucleoli. Occasionally the nuclear membranes are slightly indented. Karyokinesis is seldom seen in the mature condition.

Mitochondria.—In lower forms, and probably also in man, the cytoplasm of the interstitial cells possesses an intense affinity for mitochondrial stains, which color them diffusely, unless the differentiation is carried to an extreme. Certain cells in the corpora lutea, suprarenal, and nervous system have the same property. No adequate explanation for the phenomenon has as yet been offered, though it has been suggested that it may be due to a slightly acid reaction on the part of the cytoplasm.

Mitochondria have been investigated in man by Winiwarter (*b*) and others. They occur in the form of granules and rods, filaments being seldom seen. They are usually distributed fairly evenly throughout the cytoplasm, but may be gathered together in small clusters. The mitochondria may be stained in fresh living cells, teased out in a dilute solution of janus green, and their relations, as seen in fixed tissues, confirmed. Winiwarter claims to have seen transitions between mitochondria and crystalloids, but does not advance any satisfactory evidence as to their nature. Duesberg describes the coalescence of mitochondria, the appearance of vesicles, etc., and interprets these formations as evidences of faulty fixation.

Centrosomes.—The best description of centrosomes in human interstitial cells is given by Winiwarter (*b*). They may be either spherical or rodlike. When the nuclei are indented, the centrosomes are often found in

their concavity, as is the case in leukocytes. In cells with a single nucleus two centrosomes may occur, and in binucleated cells as many as four may be seen. There is no radial arrangement of cytoplasmic granules about the centrosome to indicate that it is a dynamic center.

Fat Inclusions.—Fat granules occur in the interstitial cells in variable amount, especially in man. They are said to increase with age, and occur in clumps distributed without apparent order in the cytoplasm.

Pigment.—Pigment granules begin to appear at about twenty-one years of age and become quite abundant. According to Lehrt the pigment is a lipochrome. Owing to the fact that there is often a sharp contrast between pigmented and non-pigmented cells in the same testicle, it has

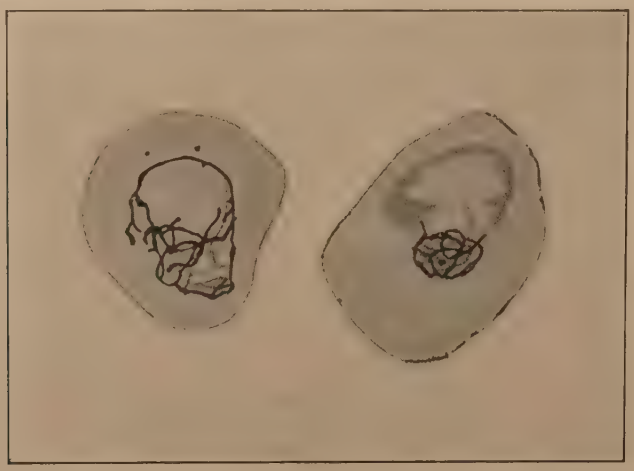

Fig. 2. Interstitial cells in the testis of the opossum showing the range of variation in the structure of the Golgi apparatus, after Duesberg.

been claimed that the pigmented cells are undergoing degeneration, though there is no noticeable difference in the size of the cells or in the nucleus-cytoplasmic ratio. Mitochondrial changes have not been studied as indicators of this supposed degeneration. In the horse fetus the pigmented cells are very discrete and are called by Bouin and Ancel (*g*) "cellules à ganulations xanthiques."

Reticular Apparatus.—Duesberg alone has studied the reticular apparatus in the interstitial cells of the opossum by means of Cajal's uranium nitrate method. He has found that it varies between the extremes illustrated in Fig. 2. Inasmuch as no trace of this complicated network can be seen in the living unstained cells, considerable caution must be exercised in its interpretation. This much may be said, however, that it must indicate some regional variation in the properties of the cytoplasm, because the location of the network is quite definite, being in close association with the centrosome.

Chromidial Substance.—While no respresentative of the chromidial substance has been discovered in the interstitial cells of the human testicle, isolated basophilic granules do occur in small numbers and have been mentioned by many authors. Their significance is obscure.

Crystalloid Inclusions.—A great variety of crystalloids are to be found in the interstitial cells of different animals. Perhaps the most notable are the crystalloids of Reinke in man. Duesberg has described more numerous and finer crystals than those of Reinke in the opossum,

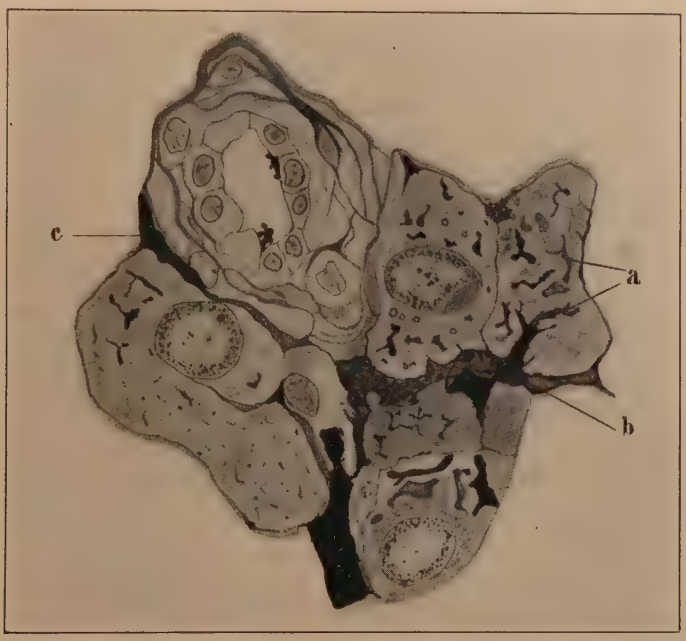

Fig. 3. Interstitial cells of testis of opossum showing (a) secretion within the cells, (b) in the intercellular spaces and (c) in the capillaries, after Duesberg.

which remind one of those found by Bensley in the thyroid of the same animal.

Specific Secretory Substances.—Many claim to have been able to detect secretion within the cells and in the neighboring blood vessels and lymphatics. It will be sufficient to mention that Mulon regards the diffuse material with intense staining reactions, above mentioned, as lipoidal in nature and the precursor of a true secretion. In this connection the striking physiological effects of the injection of lipoid extracts of the testicle (Iscovesco) are interesting and suggestive. Whether or not the mitochondria take any part in the formation of this hypothetical lipoid secretion remains to be seen.

Very recently Duesburg has discovered in fixed and stained preparations of the opossum testicle a material with quite definite staining reac-

tions, which seems to pass first into the intercellular spaces, and thence into the capillaries, as is indicated in Fig. 3. Thus far the substance in question has not been seen in fresh preparations, nor has it been specifically stained with any vital dye. Obviously, the correct method of approach is to trace this material throughout the life cycle of the interstitial cells of some common laboratory animal and ascertain, if possible, whether it varies either quantitatively or qualitatively with alterations in the physiological activity of the cells. Experimental procedures should also be resorted to. It is claimed, for instance, that removal of one testicle produces a compensatory hypertrophy in the interstitial cells of the other which may have some influence on the secretion. The chances of obtaining decisive results are good, because, in the past, investigators have paid more attention to the conditions which alter the number of the interstitial cells and have rather avoided the minute but significant alterations which occur in their structure and chemical reactions.

Physiology, Physiological Chemistry and Experimental Pathology of the Testis . . . . . *Homer Wheelon*

Introduction—Dual Function of Testis—The Evolution of Factors Characterizing Sex—Relation of Reproduction to Sex—Evolution of Genital Organs—Sexual Instincts—Nonreproductive Tissue Associated with and Establishing Sex—Relationship between the Testes and the Male Secondary Sexual Characters—The Relation of Somatic Sex Character to Secondary Sexual Characteristics—The Relationship between the Interstitial Cells of the Testes and the Secondary Sexual Characters—Effects of the X-rays on the Testis—Effects of Vasectomy on the Testis and Sex Characters—Functions of the Internal Secretion of the Testes—Influence of the Testicular Hormone upon the Development of the Generative Organs—Influence of the Internal Secretion of the Testes upon the Established Sexual Organs—Influence of the Internal Secretion of the Testes upon Nervous Structures and Their Functions—Influence of the Internal Secretion of the Testes upon Growth and Metabolism—The Pharmacodynamics of the Testes—Alterations in Sex and Their Relation to the Testes—Assumption of Male Characteristics by the Female—Sex-Intergrades—Conclusion—Purpose of the Testicular Hormone.

Physiology, Physiological Chemistry and Experimental Pathology of the Testis

HOMER WHEELON

ST. LOUIS

I. Introduction

Dual Function of Testis.—Incorporated within the testis are many cells in addition to those which are responsible for the production of spermatozoa. Among those located in the interstices between the seminiferous tubules are certain glandular elements known as the interstitial cells. These cells exercise an important influence upon the development, architecture, metabolism and activities of the body. Berthold in 1849, the pioneer in the study of internal secretions, pointed out that the testes possessed a dual function—viz., the production of spermatozoa and the elaboration of an internal secretion. Inasmuch as the interstitial cells so modify bodily structures that the purpose of the germplasm, namely, reproduction, is assured, these two functions serve a common purpose.

II. The Evolution of Factors Characterizing Sex

Relation of Reproduction to Sex.—Sex and reproduction, although intimately associated, are fundamentally unlike. Reproduction may be defined as those processes by which life is continued from generation to generation. The perpetuation of species by reproduction is accomplished in two ways—viz., by a sexual and by an asexual process. Asexual reproduction—agamogenesis—is common among the lower animals and may take the form of binary fission, spore formation, gemmation or budding. Sexual reproduction—gamogenesis—consists essentially of the union of two cells and the following development of this zygotic element.

With the development of many celled organisms—Metazoa and Metaphylia—the reproductive tissue or germplasm was early set apart from the body tissues or somatoplasm. Associated with the division of the plasms appeared reproductive tissues of two types—that giving rise to male and that giving rise to female elements. In such organisms, reproduction necessitates the expulsion and subsequent union of the cells pro-

duced by the two types of germinal tissue; consequently, the somatic changes necessary to insure fertilization were brought about. The appearance of two types of reproductive tissue associated with somatic divergences established sex. Therefore, *sex may be defined as dependent upon the sum total of the somatic characteristics and differences associated with the reproductive tissue.* Those somatic characteristics accompanying reproductive tissue which gives rise to ova, define the female sex; those accompanying reproductive tissue which give rise to spermatozoa, define the male sex. However, as will appear later, sex characters are not dependent, in all forms of life, upon the presence of active germ tissue, nor the type of reproductive tissue present.

Evolution of Genital Organs.—As animals assumed greater proportions the matter of liberating germ cells became of primary importance, hence, there arose systems of outlets—*genital organs.* In lowly forms of life the germ cells are simply extruded from the body surface. Fertilization, in such forms, is brought about by the fortuitous meeting of egg and sperm. In higher forms copulatory organs have been evolved, by means of which the spermatozoa are transmitted by the male directly to the female. Such adaptations insure the more certain fertilization of the egg.

Secondary Sexual Characteristics.—In addition to the evolution of male and female genital organs, arose other phenomena by which the sexes are characterized. Such characters were designated by J. Hunter as *Secondary Sexual Characteristics.* This term embraces all those specific differences between the male and female of the species which are not directly concerned with the processes of reproduction. Such characters are usually more elaborate in the male than in the female. Familiar examples of these characters are found in insects and vertebrates, but are rare or absent in the lower invertebrates. The horns of the stag, the mane of the lion, the great variation in color among birds, the phosphorescent organs of the firefly, and the distribution of hair in man, are typical examples of secondary sexual characteristics.

Sexual Instincts.—*Their Occurrence and Purpose.*—In addition to the structural and functional differences between the sexes have arisen the *sexual instincts.* In the lower forms these are absent and the meeting of egg and sperm remains a matter of chance. In the higher forms these instincts, or, as I prefer to call them, *"reaction impulses,"* bring the male and female together at the breeding seasons; control the behavior of the individuals towards each other—courtship, the union of the sexes—copulation—or its equivalent; and, finally, direct the various activities involved in the building of the nest and the rearing of the young.

Sex Characteristics and the Breeding Season.—In many types of animals the sexual instincts and certain somatic characters are accentuated or appear only during the breeding season. Many of the secondary sexual

characters develop only during the maturation of the germ cells; witness the cyclic growth of antlers in the stag, the building of the nest by the

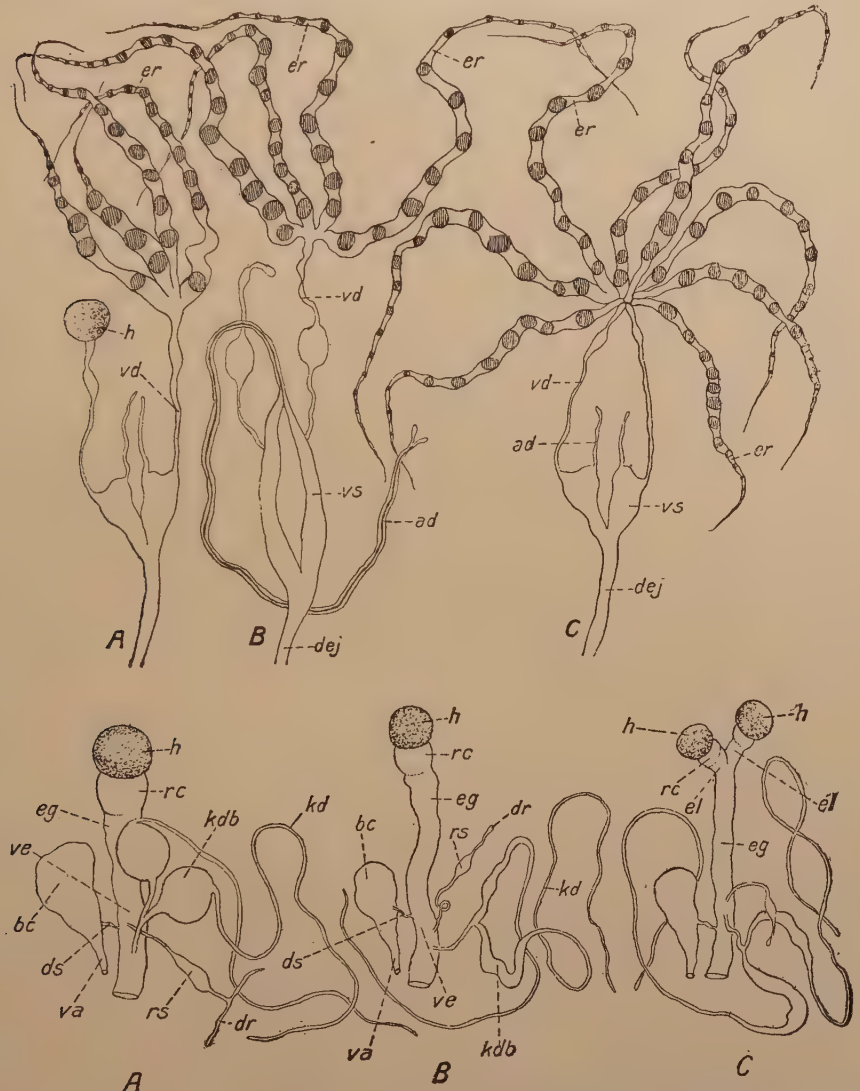

Fig. 1. Upper drawing shows transplanted ovaries grown attached to the vas deferens. A and C from Dispar, B from Quercifolia; er, oviducts; h, left testicle of a one-sided castrate; vd, vas deferens; ad, accessory male glands; vs, seminal vesicles; dej, ejaculatory ducts.

Lower drawing shows the sexual apparatus of a castrate female. A from Quercifolia, B and C from Dispar with implanted testicle grown attached to the oviduct; h, testicle; rc, regenerated calix; eg and el, egg tubes; dr, gland tubule of the seminal receptacle; rs, seminal receptacle; bc, copular bursa; ds, seminal duct; va, vagina; ve, vestibule; kd, cement glands; kdb, container of cement glands. (S. Kopéc, Arch. Ent. mech. d. Organ, Berlin, 1911-12, 33, 1-116.)

male sea-stickelback of weeds bound together with threads derived from the kidneys, the development of the specialized arm of the octopus used in the transmission of the spermatophores into the mantle chamber of the female, the peculiar activity of the salivary glands in swiftlets and crocodiles, and the periodic activity of the anal gland of snakes and the cloacal glands of the tortoise and other reptiles. All characters of this type either aid in the processes of mating or enable the sexes more easily to detect each other.

III. Nonreproductive Tissue in relation to Sex

1. Relationship Between the Testes and the Male Secondary Sexual Characters.—*Relation of the Testes to Sex Characters in Insects.*—Whether or not the sex glands affect the sexual instincts and secondary sexual characters depends upon the forms of life selected for study. For instance Oudemans, Meisenheimer, and Kellog have shown that the reproductive tissue of insects in general appears to have no influence whatever upon the development of sexual characters, although sex dimorphism is well marked. The removal of the ovaries and testes from the caterpillars of gipsy moths in no way alters the development of sexual differences. Furthermore, castrated female caterpillars into which the sex glands of young males have been grafted develop into characteristic female moths. Castrated male caterpillars carrying ovarian transplants develop into chrysilids, and finally into moths. These moths show no characteristics whatever of the female. Dissection of the fully grown moths demonstrates that the ovaries have formed many connections with the outlets of the male organs left behind (Kopéc (*a*) (*b*)). Testes grafted into female bodies develop and produce spermatozoa (Fig. 1). Crampton has further shown that transplanted heads of the opposite sex develop in accordance with their original sex. Such striking observations show clearly that, in these species at least, the reproductive tissue of either sex will develop in the body of the opposite sex without in any way influencing the secondary sexual characters of the individual. It is necessary, therefore, to study these characters apart from the influence of the sex glands.

Certain insects, however, do show morphological and instinct changes following gonadectomy, but such changes do not appear to result directly because of the loss of the gonads. For instance, Kornhauser has shown that male *Thelia bimaculata* parasitized by dryinid *Aphelopus theliae* assume the pigmentation of the female and increase in size. Also small spines on the abdominal sclerites take on the arrangement characteristic of the female. The genital appendages are reduced but never changed into those of the opposite sex. Nevertheless, a normal testis with spermatozoa may be present in parasitized males showing changes toward the female type and a perfect female soma may be associated with a normal

male gonad composed of cells characteristic of the male complex of chromosomes. Parasitized females show no assumption of male pigmentation nor do they change in size.

Relation of the Testes to Sex Characters in Crustaceans.—Among the crustacea the relation between the testes and sexual characters is quite pronounced. According to Potts (*a*) (*b*), Smith and others, certain male crabs which have become parasitized by other crustaceans, develop the secondary sexual characters of the opposite sex. The parasite after attaching itself develops in a manner which brings about partial or complete destruction of the reproductive tissue of the host. The males so infested show every degree of modification toward the female type; the legs are small, the stylets reduced, the abdomen broad, and typical biramous appendages appear. Infested females, on the contrary, although their ovaries are destroyed, undergo no change toward the male type, although the abdominal appendages are somewhat reduced. Inasmuch as the testes of the male suppress the development of the secondary sexual characters that ordinarily appear only in the female, there is, in these crabs, a relationship between the generative tissue and the sexual characters.

Relation of the Testes to Sex Characters in Birds.—In birds the relationship between the gonads and plumage is apparently the reverse of the relationship described above in the crab. Female fowls and pheasants often assume, in their old age, the characteristics of the male. Similar alterations occur as the result of diseased ovaries. The removal of the ovaries of young chicks and ducks also permits of the development of secondary sexual plumage like that of the male. Also, castration of the Seabright cock, the plumage of which is like that of the female, results in plumage like that of the ordinary male fowl. The plumage of cocks does not appear to be altered by castration; the combs, spurs and wattles, however, are less highly developed (Goodale, Boring and Morgan, Walker). Therefore, it may be argued that the female possesses the potential ability to assume full male plumage, but does not do so in the presence of a normally functioning ovary; hence, the ovary in some way inhibits or prevents the establishment of certain sexual characteristics which appear normally in the male. However, Goodale has shown that different parts of the soma react differently to the influence of the gonads—that is, some characters such as size in females, voice, mandible color in ducks, and certain phases of behavior, are independent of either ovary or testis, while others depend entirely or to some extent upon the proper functioning of the gonads. For instance, the comb, wattles, fat disposition, size in males, summer plumage, and some instincts in ducks are influenced by the testis, while plumage, form, color, and some phases of behavior are influenced by the ovary. Therefore, the secondary sexual characters in birds are not equally affected by the primary sex organs.

Relation of the Testes to Sex Characters in the Triton.—Further evi-

dence of the dependence of certain somatic structures upon the gonads is afforded by the triton. Each year the male develops a special comb-like fin on the back and tail. Bresca has shown that if this comb is removed it regenerates in normal males, but less perfectly in castrates. Castration, after the development of the fin is initiated, retards its further development. A piece of the dorsal fin of the female transplanted to a normal male, develops into the characteristic male comb. Therefore, in this case, the testes apparently affect tissue of either sex, and determine its growth into a character normally associated with maleness.

Relation of the Testes to Sex Characters in Mammals.—In certain mammals it has been clearly shown that the secondary sexual characteristics either do not appear, or develop imperfectly if the sex glands are removed. In birds, mammals, and certain other animals, there is also a close relationship between sexual maturity and the appearance of the sexual characters.

Observations on horned animals are of special interest in this connection because they show a dependence of horn formation upon the functioning of the gonads in varying degree. An illustration of such a relation may be stated in the words of John Hunter: "Castrate a young bull and his neck will grow; but the hair of his forehead and his horns will grow to the length of those of a cow, or longer—steers. Take a boar, and his tusks will not grow." In the eland and reindeer both sexes possess well-developed antlers, the perfect development of which is not hindered by castration. Neither does castration cause them to be shed. In these animals horn formation is in no way dependent upon the gonads. On the other hand, in case of the deer, castration of the young male before the knobs of the antlers have appeared prevents the development of antlers. Castration after the beginning of antler formation results in the development of small, permanent, velveted stumps or peruke antlers. Removal of the testes in the adult stag, after the antlers are fully developed, results in their precocious shedding; and if new antlers form, they are imperfect and are never renewed. Therefore, in the deer, there is an intimate relationship between the cyclic development of antlers and the reproductive tissues. In the Dorset sheep, the horns of the male are very much heavier and larger than those of the female. Castration of young males leads to horn formation comparable to that of the female. In these animals factors for horn formation are sufficient to cause them to develop to the point reached in the female. The further development of horns in rams is, therefore, associated with and dependent upon the presence of the testes. Hence, only the size and weight of horns in these sheep can be considered as secondary sexual characters, and that alone in the male. In Herdwick sheep the rams possess large spiral horns while the ewes are hornless. The growth of horns ceases, following gonadectomy of the male. However, the spaying of females does not result in the development of horns,

although small scurs may appear. Therefore, horns, in this type of sheep, must be considered as secondary sexual characters which are dependent upon the proper functioning of the testes.[1]

Perhaps the most convincing evidence of the dependence of the somatic structures related to sex upon the primary reproductive organs is afforded by the results of cross-grafting of gonadal tissue into previously castrated animals. Steinach and Sand have clearly shown that the ovaries of the female rat and guinea pig can be successfully grafted into previously castrated males. These "feminized males" develop characters peculiar to

Fig. 2. Photograph of guinea pigs showing the effects of "feminization" on somatic development. A, castrated brother; B, normal virgin sister; C, "feminized" brother; D, normal brother. (Steinach and Holzknecht, 1916, Fig. 2, p. 494.)

the female. The mammary glands, rudimentary in the male, become greatly enlarged, the hair assumes the texture of the female, the size and skeleton takes on proportions resembling those of the female more nearly than those of the normal or castrated male (Fig. 2). "Masculinized females" take on the somatic characteristics normally associated with maleness (Fig. 3). In these cases, as in that of the triton, somatic structures respond, not to their previous habit, but to the type of gonadal influence exerted upon them.

The striking alterations in growth and development, following castration of men, with resulting eunuchism, probably afford the earliest recognized information regarding the influence of the reproductive tissue on the body. Gonadectomy, prior to the advent of puberty, prevents the complete development and the perfect functioning of the nervous system,

[1] The relation of horn formation to the gonads has been thoroughly reviewed in the works of Biedl, Geddes and Thompson, Marshall, and Morgan.

the generative tract, and the characteristic male hirsutis. It arrests the proper development of the chest and pelvis, preserves the high-pitched voice of youth, and retards the closing of the epiphyses (Tandler and Gross).

2. The Relation of Somatic Sex Characters to Secondary Sexual Characteristics.—The above discussion, in brief, shows the relationship of the gonads to the somatic sex characteristics. The phrase "somatic sex characteristics" is used advisedly, for it is apparent that sex dimorphism is not maintained in all forms of animals because of the type of repro-

Fig. 3. Photograph of guinea pigs showing the effects of "masculinization" on somatic development. A, "masculinized" sister; B, castrated sister; C, normal sister; D, normal brother. (Steinach and Holzknecht, 1916, Fig. 1, p. 492.)

ductive tissue present. Somatic sex differentials in lower forms and, to a certain degree, among the higher animals are absolutely independent of gonadal influence of either sex. Such characters, therefore, should not be classed as Secondary Sexual Characters, but rather as *Sex Associated Characters.* On the other hand, those sex differences which depend upon the presence of functioning gonads are properly classed as Secondary Sexual Characteristics because, as the term implies, they are dependent upon the primary sex organs for their development and maintenance. Sex associated characters are as old as sex itself, but secondary sexual characters appeared relatively late in the evolution of sex. Moreover, these characteristics appeared gradually, and evolved along different lines in the various types of animals. Therefore, we may justly conclude that in many forms of life certain characteristics of sex are dependent upon the presence of normal reproductive organs, and that certain cells respond to

further development and functionation only in their presence. However, I would not leave the impression that any tissue in itself is sufficient to establish sex. The sex of the subsequent individual, in all probability, is determined at the time of fertilization, but, in certain animals, the fullest degree of maleness or femaleness is assured only by the presence of the reproductive tissue laid down in the embryo.

3. The Relationship Between the Interstitial Cells of the Testes and the Secondary Sexual Characters.—The question now arises, how do the sex glands exert their influence upon the development and maintenance of somatic structures dependent upon them? According to the older physiologists this is accomplished by influences exerted through the nervous system (Nüssbaum). However, the results obtained by the transplantation of gonadal tissue into previously castrated animals prove this theory untenable. Numerous observations both on man and animals have established the fact that the effects following gonadectomy are, to a great extent, obviated by successful transplantation of gonadal tissue. Preparations and extracts of reproductive tissue serve a similar purpose. Obviously, therefore, the gonads exert their influence by means of substances liberated into the somatoplasm. Hence the testes may be considered as organs of internal secretion. The exact manner in which the gonads exert their influence upon the somatic structures, however, remains to be demonstrated.

Castration necessitates the complete removal of the primary reproductive organs; hence, results obtained by such procedures may be interpreted as due either to the loss of spermatogenic tissue, or other structures present in the testes. Therefore, a study of the effects of castration simply locates the organ, the presence of which is so necessary to the proper development of masculinity. Observations upon the effects of testicular transplants and the administration of extracts are open to the same criticism. Such observations, therefore, throw no immediate light upon the solution of the present problem.

At present there is no evidence that the secondary sex characters are in any way associated with the activities of the sperm-producing cells. On the contrary, there is a wealth of evidence which indicates that these characters are dependent upon certain cells lying in the interstices between the seminiferous tubules, viz., the Interstitial Cells.

Histology of the Interstitial Cells of the Testis.—The interstitial cells of the testis were first described by Leydig in 1850, and are commonly referred to under his name. He characterized these structures as clear, round cells, analogous to embryonic connective tissue, vacuolated and containing fat and pigment granules. Kölliker in 1854 also described these cells and further demonstrated their presence, not only in the interstices of the seminiferous tubules, but also in the mediastinum and connective tissue septa of the testis, and under the tunica albuginea.

The interstitial cells, according to Bouin and Ancel, Chapin, Allen, and Whitehead, appear in the primitive genital tract and become functional before the spermatic cells are fully differentiated. Whitehead has shown clearly that the intertubular tissue of the testis of the pig embryo in stages immediately preceding the appearance of interstitial cells is a mesenchymal structure derived from the mesothelium of the genital ridge. Histologically, this tissue is a connective tissue syncytium consisting of cells and an exoplastic network of fibrils. The cells are scarcely more than naked nuclei, though some have a small collection of cytoplasm at one pole. From the cells of this tissue interstitial cells are developed by growth of cytoplasm. At first they are markedly branched; some of the branches are connected with the general exoplastic network, so that the cells retain the syncytial arrangement of their ancestors. They increase rapidly in number and size and soon lose their branches.

In the pig the interstitial cells pass through two phases of growth with a phase of atrophy intervening. Growth is very rapid from their appearance in the embryo 2.4 cm. long, until the length of 3.5 cm. is reached. This is followed by the phase of atrophy, during which the cells return almost to their first stage of naked nuclei. This process reaches its acme in the embryo 14 cm. long and synchronous with it there is an extensive growth of the seminal tubules, so that they are greatly convoluted and the intertubular spaces correspondingly narrowed. In the embryo 20 cm. long the interstitial cells enter upon their second phase of growth which attains its maximum in the pig 28 cm. long, or very near to term. At this time the cells are enormously increased and constitute the predominating feature of the microscopic picture.

In the adult the interstitial cells appear as rounded or polygonal elements which vary greatly in different species and from time to time in the same individual (Hofmeister). The nucleus usually lies eccentrically and is surrounded by a condensed endoplasm which merges into a less dense, vacuolated ectoplasm. Soluble and insoluble pigments are present (Regaud, von Ebner, Mott, Duesberg and Whitehead). Lipoid, although variable in amount, is never entirely absent from these cells and may appear in the form of phosphatid lipoid material, cholesterin esters, or neutral fat (Hanes and Rosenbloom, Whitehead, and Rasmussen).

In man, according to Ishibashi, the interstitial cells are of variable structure according to age. They are conspicuously numerous in children, and at certain stages closely resemble fibroblasts. Mott observed 100 autopsy cases from birth to 86 years, and found that the interstitial cells appeared in great numbers at birth and contained lipochrome material. At puberty the tubules are closely approximated and the interstitial lipoid is abundant. Cases dying before puberty (of chronic diseases) demonstrate an arrest of granules in the interstitial cells.

In males having a rutting season spermatogenesis occurs only at this time. This periodic activity is usually associated with a great increase in the size of the testis, and in certain forms, most rodents, insectivoria, and bats, with the descent of this organ from the abdomen into the scrotum. According to Marshall, LeCallion and others, a part of this seasonal increase in the size of the testis is due to an increased proliferation of the interstitial cells. Watson has shown that the interstitial cells demonstrate a marked development in the non-œstrous periods, and decrease in number as the testis increases in size, while spermatogenesis proceeds. In the hibernating marmot, according to von Hansemann, spermatogenesis ceases and the interstitial cells almost completely disappear. With the assumption of spermatogenesis in the spring the interstitial cells reappear in great numbers. Rasmussen (*a*) (*b*) observed that spermatogenesis in the woodchuck progresses slowly during hibernation and then increases suddenly for a month at the termination of this time. This period is now followed by an almost complete absence of spermatogenesis. Following this, spermatogenesis increases again until the following year. The development of interstitial cells, on the other hand, does not occur except during the Spring and early Summer. They reach their greatest size only after the Summer and Autumn.

It appears that all forms of life do not possess interstitial cells in their testes, for, as Pézard has shown, adult Orpington fowls and golden pheasants do not show the presence of these cells even during the period of greatest sexual activity. However, Boring and Pearl state that interstitial cells are demonstrable in male chicks just hatched, but not in adults.

The belief that the interstitial cells formed the internal secretion of the testes was first based upon the finding, by Rienke, of certain crystals in these cells and in the lymphatics of the human testis. These crystals, however, have not been found in other animals. On the other hand, certain experimenters advanced the theory that the generative tissues alone were responsible for the production of the testicular hormone (Nussbaum). In support of this theory is cited the synchronous development of rutting organs with the most rapid production of spermatic cells. It has been further contended that it is the action of the spermatogonia, which at the breeding season stimulates the production of the rutting organs. Such theories were once justifiable because of the belief that the interstitial cells were trophic elements, whose function it was to take up nourishment from the blood stream and transmit it to the sustentacular cells (Regaud, Plato).[2]

Interstitial Cells and the Testicular Hormone.—Many facts demonstrating that the interstitial cells are responsible for the internal secretion

[2] For an excellent review of the older theories see the paper by Hanes, 1911.

of the testes are revealed by the studies of the selective action of the *x*-rays, vasectomy, and undescended testes, i. e., cryptorchism.

Effects of the X-rays on the Testis.—The studies of Albers-Schönberg, Bergoine and Tribondeau, Regaud and Dubreuil (*a*) (*c*), Gordan and Simmonds (*a*) have clearly shown that the *x*-rays exert deleterious effects upon the male genital glands. Male rabbits and guinea pigs exposed to the action of these rays and later given ample opportunity to copulate with unexposed females fail to impregnate them. However, such males demonstrate normal desires and potency. Microscopic examination of the testes of such males shows a reduction or absence of spermatogenesis. Many observers have recorded the absence or the infrequency of spermatozoa in the semen of men following exposures of various degrees to the *x*-rays. Such individuals do not develop marks of impotence or loss of sexual instincts (Brown). Furthermore, the exposure of males possessing well marked secondary sexual characters to the influence of the röntgen rays in no wise alters such characteristics. On the other hand irradiation of the whole body of white rats, according to Hewer (*b*), when the animals are very young does hasten sexual development in the male.

Histological studies have clearly shown that the *x*-rays, while destroying the germ cells, fail to alter the interstitial cells. However, Simmonds has shown that even after prolonged exposure, isolated seminiferous tubules remain intact, and, if the animal lives a sufficient length of time, regeneration of the germ cells occurs and spermatogenesis is restored. Furthermore, destruction of the sperm producing cells is invariably accompanied by proliferation of the interstitial cells, which condition disappears after regeneration of the spermatic cells. The sustentacular cells remain unaffected following radiation. Such observations as these clearly show that the production of sperm is not essential to the integrity of the secondary sexual characters and the sexual instincts.

Effects of Vasectomy on the Testis and Sex Characters.—Ligation of the vas deferens in immature animals does not inhibit the beginning of subsequent spermatogenesis. The results of such operations, according to Griffiths, are seen as secondary consequences at puberty, when the formation of semen normally occurs. Vasectomy, either unilateral or double, does not inhibit the growth of the prostate or other sex characters, but unilateral vasectomy will prevent the full development of the testis on the side of the operation, as compared in size with the organ on the unoperated side (Marshall). According to Bouin and Ancel (*c*), Griffiths, Myers, Wheelon, and Kuntz ligation of the vas results in the cessation of spermatogenesis; spermatocytes and spermatogonia degenerate, and after some months all spermatogenic elements disappear. At first there is no apparent change in the appearance of the sustentacular cells—Sertoli cells —of the seminiferous tubules; but these, too, ultimately disappear (Tournade). On the contrary, the interstitial cells retain their morphological

and functional integrity indefinitely, and as long as these remain, alterations of the stigmata of sex do not occur (Myers, Wheelon). If these cells disappear from the testes the results are the same as those following castration. Recent works indicate that occlusion of the vas, although causing primary degenerative changes in the sperm producing tissues accompanied by hyperplasia of the interstitial cells, does not prevent the subsequent appearance of sperm cells in the uriniferous tubules (Steinach, Kuntz, Wheelon).

The operation of vasectomy upon male horses in place of castration does not produce the results of castration; these animals retain all of the sex characteristics of the stallion. Similar results are observed in cryptorchids from which the greatly enlarged epididymis instead of the testis is removed. Simple occlusion of the vas in Herdwick rams does not prevent the normal development of the secondary sex signs (Shattock and Seligmann). Unilateral castration accompanied by ligation of the opposite vas results, within six months, in a diminution of the testis left *in situ;* the seminiferous tubules carry but few spermatogonia, and the sustentacular cells remain unchanged. At the end of a year the testis is composed almost entirely of extremely hyperplastic interstitial tissue; the seminiferous tubules are greatly shriveled and the sustentacular cells degenerated. However, sex characters remain as before the operation.

Such observations are of special interest in that both sperm producing tissue and sustentacular cells are destroyed without destruction of the interstitial cells. The fact that the accessory sexual organs and the secondary characters of sex appear and are maintained in association with the interstitial cells alone is strong evidence in support of the theory that these cells, and not the sperm producing or nutrient cells, are responsible for the hormone production of the testes. The loss of interstitial cells and castration, therefore, are equivalent as far as the development and maintenance of secondary sexual characters are concerned.

Cryptorchism and the Interstitial Cells.—Hyperplasia and hypertrophy of the interstitial cells appear always to accompany both imperfect development and secondary atrophy of the seminiferous tubules (Dürck). Cryptorchid animals, or those possessing imperfectly descended testicles, may be considered intermediate between castrated and normal individuals in regard to the genital glands, sexual instincts and characters. Not infrequently there is a minimal development or an entire lack of interstitial cells; consequently the apparent degree of maleness is determined by the degree of development of these cells (Bouin and Ancel, Doolen, Regaud and Policard). Observations upon cryptorchid pigs, the testicles of which have remained at a primitive stage of development, show an absence of the sustentacular cells, while the interstitial cells are well developed (Fig. 4). Such animals are typical males in appearance, and the genital tracts are fully formed. Bilateral

arrest of the testes associated with a lack of development, as a rule, means absolute sterility without loss of virility. In such cases the spermatogenic function is in abeyance, yet the production of an internal secretion determines the masculine characters. A retained testicle which is otherwise normal is not likely to atrophy before the period of puberty, hence, as a matter of clinical practice, corrective measures should be undertaken, prior to puberty, in order to prevent degeneration of the spermatogenic function

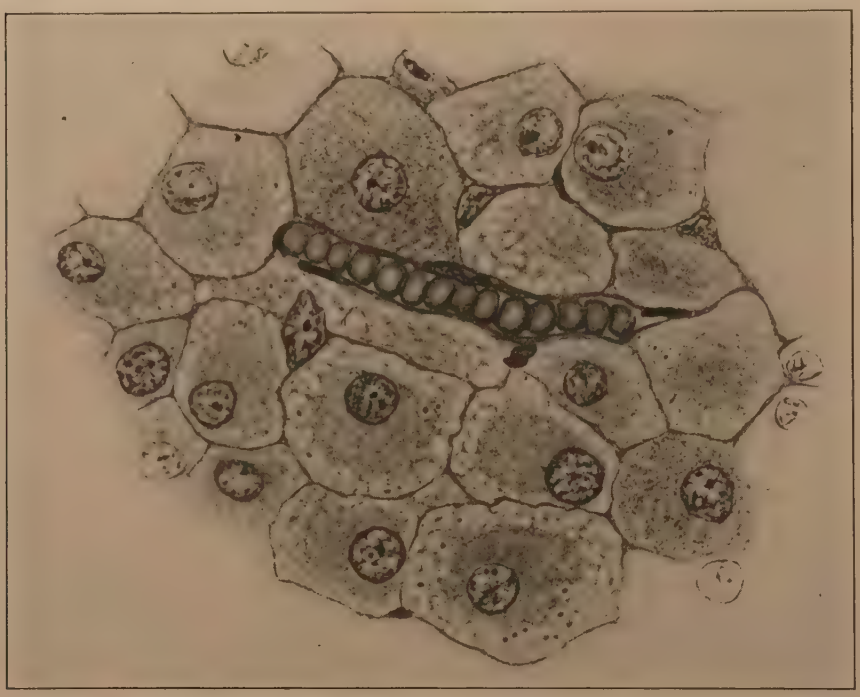

Fig. 4. Section of cryptorchid pig testicle showing the interstitial cells surrounding a capillary. Some of the cells are homogeneous throughout, but some of them show a dense endoplasm and a vacuolated ectoplasm containing definite granules. × 1,000. Zenker's fluid, hematoxylin and eosin. (Hanes, 1911, Plate xxx (Fig. 1).)

(Keyes, Corner, Eccles). If, however, complete sclerosis of the testes occurs, or there is a complete suppression of the spermatic cord, the individual is sterile and remains sexually undifferentiated (Griffiths, Eccles, Hanes, Félizet and Branca). In such cases the penis remains small and appears shrunken; hair about the pubes shows a feminine arrangement, the pelvis retains the infantile type, and the larynx and voice remain as in boys; occasionally the mammæ show hypertrophy—gynecomastia (Hammett).

Histological preparations of the cryptorchid pig testis, according to the findings of Hanes and Rosenbloom, Eccles, and Whitehead, show the presence of an excessive number of interstitial cells. These cells are

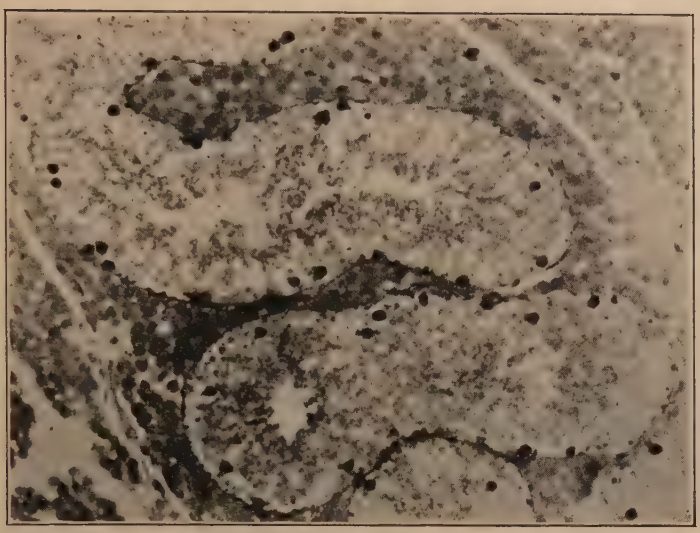

Fig. 5. Section of normal pig testicle in active spermatogenesis. The droplets of neutral fat lying in the Sertoli cells form an outline of the seminal tubule. Numerous small droplets of fatty material are seen toward the lumen. Altmann's fixation (osmic acid and potassium dichromate); stained with Bensley's neutral gentian. (Hanes and Rosenbloom, 1911, Plate xxxvii, Fig. I.)

Fig. 6. Section of cryptorchid pig testis, stained with Sedan III and hematoxylin. The tubules are much smaller than in the normal testicle and are lined only by a layer of Sertoli cells which contain a large number of neutral fat droplets. No sperm forming cells are present. The Leydig (interstitial) cells are seen, on comparison with Figure 5, to be greatly increased in number.

Figures 5 and 6 are microphotographs taken under exactly the same magnification.

usually larger than those of the normal testis (Fig. 5), otherwise their structure is the same. The seminiferous tubules show marked abnormalities; their basement membrane is thickened, and lined only by a single layer of sustentacular cells. Sperm producing cells are not found in the adult cryptorchid testis (Fig. 6). Similar pictures are seen in the cryptorchid human testis (Freiberg). In very young cryptorchid testes, however, large clear primary sperm cells are seen, but these apparently do not develop, and soon disappear.

Fig. 7. The urogenital organs of a normal pig. (Hanes, 1911, Plate XXXIV, Fig. 8.)

No distinction can be made between the genitalia of normal and cryptorchid animals possessing functional interstitial cells (Figs. 7, 8). Complete sclerosis of the testes and castration, on the other hand, result in immature development of the genitalia (Fig. 9). Hence, since the sexual characters develop quite normally in the absence of sperm-forming cells, they may be eliminated as possible factors in the elaboration of an internal secretion by the testes.

The sustentacular cells, in some instances, remain long after complete degeneration of the sperm-producing cells in cases of vasectomy as well as in testicular transplants and in cryptorchid testes. The following considerations, however, relieve these cells of any responsibility in the production of the testicular hormone.

The interstitial cells sustain an intimate relationship with the rich capillary meshwork of the testis; they surround the capillaries in their course to the seminal tubules, and are bathed in the large intertubular lymph spaces. Hence, the morphological position of the interstitial cells suggests the possibility of an intimate relation with the body fluids or distributors of internal secretions. Further, as spermatogenesis proceeds in the normally functioning testis, the large fat droplets present in the basal portion of the sustentacular cells divide into smaller portions, pass centralward into the prolongations of the cells and then on into the

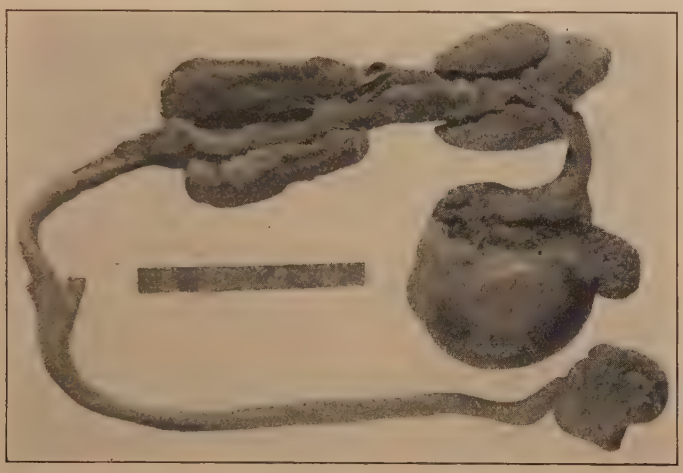

Fig. 8. The urogenital organs of a monocryptorchid pig (the other testicle had descended normally and had been removed). (Hanes, 1911, Plate XXIV, Fig. 9.)

The three photographs are taken to scale and show the bladder, prostate, seminal vesicles, glands of Cowper, and penis. The organs of the castrated pig (Fig. 9) are small and atrophic, whereas the organs of the cryptorchid pig (Fig. 11) are as well developed as in the normal animal (Fig. 10).

spermatids (Hanes). During this migration the neutral fat changes to a lipoid. Spermatogenesis is absent in the cryptorchid testis, hence, if the function of the sustentacular cells is to transmit nourishment to the spermatids, the absence of spermatids from the seminal tubules should result in the accumulation of fat in the sustentacular cells. Histological preparations of cryptorchid testis stained to show fat demonstrate that the sustentacular cells are loaded with fat droplets. Chemical analyses of cryptorchid and normal testes further confirm this view. The fat content of the dried weight of normal pig testes, according to Hanes and Rosenbloom, is 19 per cent, while that of cryptorchid testes is 31 per cent. Hence it may be concluded that fat accumulates in the sustentacular cells of the cryptorchid testis because of the absence of spermatogenic cells which normally utilize this substance.

Interstitial Cells and Eunuchoidism and False Hermaphroditism.—Further evidence of the dependence of the sex characters upon the interstitial cells is afforded by a consideration of the characters and condition of the gonads in cases of eunuchoidism and false hermaphroditism. In such individuals the loss of sexual desire and characters is in proportion to the degree of withdrawal of the gonadal influence. Those showing complete loss of sexual desires and incomplete stigmata of masculinity demonstrate marked atrophic alterations in the testes. Often the seminiferous tubules are solidified cords demonstrating marked degenerative changes. The interstitial cells are usually few and abnormal in appearance. Individuals showing such atrophic changes of the testes are the equivalent of castrates, for they show neither functional spermatic nor

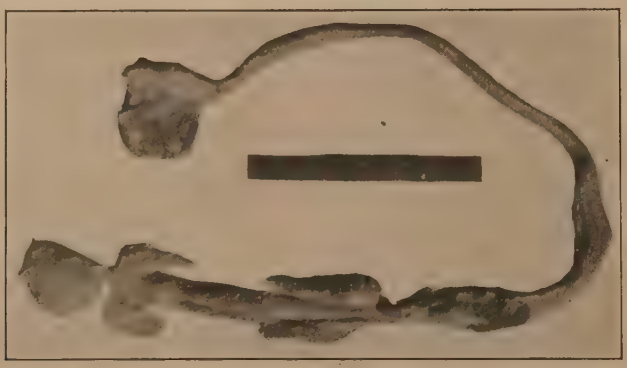

Fig. 9. Photograph of the urogenital apparatus of an adult castrated pig. (Hanes, 1911, Plate XXXIV, Fig. 7.)

interstitial tissues. As pointed out above, the disappearance of spermatic tissue or the sustentacular cells does not in any way alter the normal progress of sexual characteristics. That it is the degeneration of the interstitial cells, rather than that of the spermatogenic tissue, which causes the absence of libido and sex characters in the eunuchoid and false hermaphrodite, is substantiated by the evidence from infertile hybrids and cryptorchid individuals. In these, spermatogenesis is incomplete or wanting, but the interstitial cells are normal, and as long as these latter cells remain functional the characters of sex and libido are normal (Jordan, Climenko and Strauss, Falta, Biedl, and Cushing).

The facts set forth in the above discussion demonstrate that the male secondary characters of sex are not dependent upon the formation or nourishment of spermatids; therefore, the elaboration of an internal secretion by the male reproductive organ appears to be the sole function of the interstitial cells. It is true that weighty arguments have been set forth to reverse the above statement. An evaluation of available data, however, justifies the contention set forth relative to the interstitial tissue.

IV. Functions of the Internal Secretion of the Testes

1. Influence of the Testicular Hormone upon the Development of the Generative Organs.—A consideration of the embryology and subsequent development of the generative organs shows that the interstitial cells affect their development. For convenience the developmental relationship existing between the somatoplasm and germplasm may be considered under the following headings: Primary and Secondary Undifferentiated Stages, and Primary and Secondary Differentiated Stages (Wheelon).

Undifferentiated Stages.—In the higher forms of life the presence of the germplasm manifests itself only after marked development of the somatoplasm. In human embryos up to a length of 14 mm. sex cells, though developing, are not recognizable histologically. Hence, this period may be called the Primary Undifferentiated Stage of sexual development.

The Secondary Undifferentiated Stage is illustrated in embryos from 14 to 24 mm. in length, in which aggregates of cells are recognizable as testes or ovaries. At this time the Wolffian and Müllerian ducts, which later give rise to either male or female internal secondary sex organs, are being laid down. Such embryos, although possessing well established reproductive cells, are sexually neutral or somatically indifferent, hence the primordia of the genital glands are independent of the generative organs.

Differentiated Stages.—Immediately following the secondary undifferentiated stage, vascularization of the sex glands occurs and the embryo enters upon the Primary Differentiated Stage. This period, beginning in the 24 mm. embryo, is continued to puberty. The Müllerian and Wolffian ducts undergo marked alterations; either the Wolffian ducts continue development and form the excretory ducts of the testes, or the Mülleran ducts partially fuse to form the uterus and tubes. When the further development of either of these pairs of ducts is determined the development of the other pair ceases and soon retrogressive changes ensue. Because of these somatic alterations the sexually undifferentiated character of the embryo is lost.

Vascularization of the gonads and sex differentiation are intimately associated, hence it may be assumed that a *principe* is liberated from the germ cells or from tissues closely associated with them at the reception of a blood supply which acts in such a manner as to bring about sex differentiation. Sex organs are not present until differentiation has taken place and the embryo has assumed male or female characteristics, hence sex cannot be ascribed to the embryo until genital organs appear, even though reproductive tissue of one sex is present. Granting that the sex of the ovum is determined at the time of fertilization, sex, as such, does not appear until

either stimulating or inhibiting factors have acted upon the sexually neutral or indifferent somatoplasm.

Observations on the Free-Martin.—This view is substantiated by the observations of Lillie on the *free-martin* (Figs. 10, 11, 12). As a rule the

Fig. 10. Reproductive organs of fertile free-martin 23.3 cm. long. × 4/3. The chorion of the twins was single with a narrow connection between the two halves. Presumably no vascular anastomosis. The male was 26.5 cm. long, nearly 80 per cent heavier than the female, and its skin was unpigmented, whereas the female was darkly pigmented. 1, ovary; 2, left horn of uterus; 3, round ligament; 4, vagina; 5, clitoris; 6, neck of allantois. (Lillie, 1917, Fig. 8, p. 430.)

female of two-sexed twins of cattle is sterile. The internal reproductive organs in these sterile females are usually predominatingly male in character; the external organs, female in type (Fig. 11). The Müllerian ducts are usually diminished or absent; the Wolffian ducts are often developed into quite typical vasa deferentia and the gubernaculum develops as in the male. The gonad is testis-like in form and structure by reason of the complete

suppression of the ovarian cortex and hypertrophy of the homologues of the seminiferous tubules (Chapin). The general appearance of the adult free-martin is intermediate between that of the male and female, re-

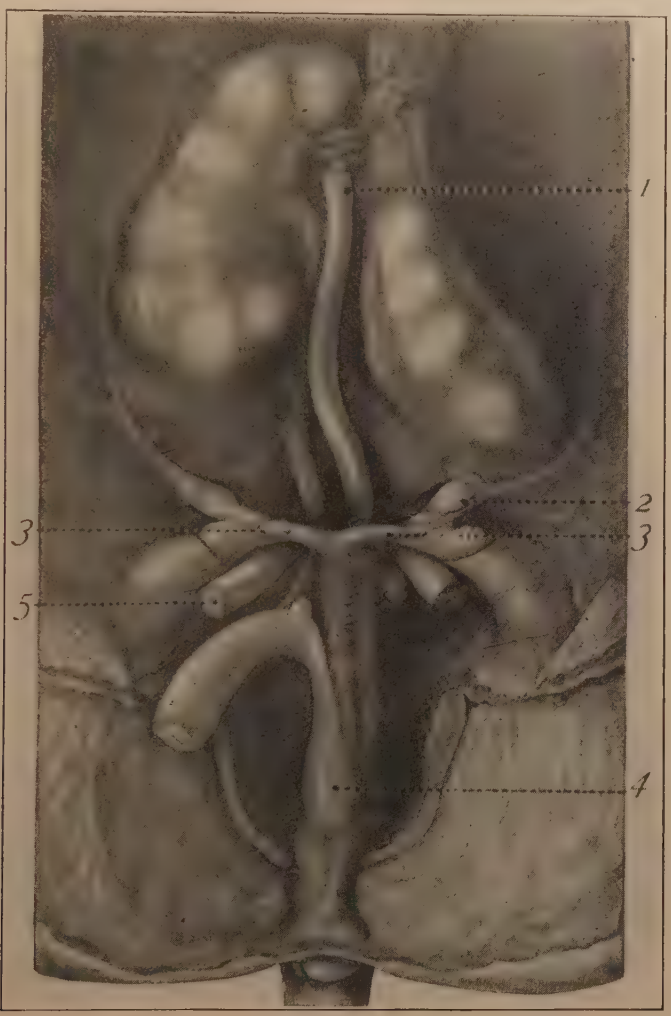

Fig. 11. Urogenital system of sterile free-martin 27 cm. long. × 4/3. From two sexed pair 14. Although this case is beyond the stage in which the testes of the male normally enter the saccus vaginalis, the rudimentary ovaries are here in the body cavity. In this case there appear to be rudiments of the cornua uteri. 1, rectum; 2, gonad; 3, cornua uteri; 4, urogenital sinus; 5, umbilical artery. (Lillie, 1917, Fig. 26, p. 448.)

sembling the ox or spayed heifer. The twin bull, on the other hand, is normal and fertile (Fig. 12). The free-martin condition is found only in association with a male twin the chorion of which has formed vascular anastomosis with the chorion of the female. Hence, the presence of a male

twin and a common chorion stand in some kind of etiological relationship. Furthermore, the fusion of the chorions occurs at or about the time of

Fig. 12. Normal male 26 cm. long; from twin one-sex pair. × 4/3. Single chorion, constricted between the two fetuses. This figure shows the entire urogenital system; the gubernacula have entered the scrotal sacs. The testes are drawn into the vaginal sacs. The disposition of the teats for the normal male should be noted. 1, rectum; 2, vasa deferentia; 3, epididymis; 4, testis; 5, urogenital sinus; 6, gubernaculum withdrawn from scrotal sac; 7, cut end of umbilical cord; 8, prepuce; 9, wall of penial sheath; 10, penis; 11, vesiculæ seminales; 12, teats; 13, allantois; 14, gubernaculum in scrotal sac; 15, retractor muscle of penis. (Lillie, 1917, Fig. 12, p. 434.)

the beginning of sex differentiation. Hence, it may be concluded that the sterile free-martin is zygotically a female modified by the sex hormone of the male twin which circulates in the vessels of both individuals during

fetal life. The fetal membranes of twin sheep are also fused, but there is no vascular anastomosis. The females in these two-sexed twins are normal anatomically and functionally. The same is true of two-sexed twins in cattle if the chorions do not fuse (Fig. 10).

In mammals the interstitial cells are present in the testes from the very beginning of sex differentiation. In the ovary differentiation occurs later than in the testes because the first generation of ingrowths from the germinal epithelium—a true homologue of the seminiferous tubules of the male—forms only the medulla, while the cortex is formed from a second generation of ingrowths. The testes of the male of two-sexed twins therefore are present and exert an influence before the ovaries have developed their structure or function. Such a condition, of necessity, brings about suppression of the specific ovarian tissue from the very beginning (Lillie, Chapin).

Such an explanation of the factors resulting in the formation of the free-martin lends weight to the argument of van der Broek, who contends that the cause of pseudohermaphroditism is an imbalance of gonadal hormones between the mother and fetus.

Heterologous Transplants and Development of the Generative Organs. —The influence of the sex hormone upon the generative organs is further shown by the results following the transplantation of a gonad of one sex into an immature and previously castrated animal of the opposite sex. As previously stated, Steinach, Sand and Moore have been able to change completely the instincts and to a great extent alter the sex characters of rats and guinea pigs by the substitution of a gonad of the opposite sex in pre-adolescent castrates. Further than this, Sand, and later Steinach succeeded in establishing simultaneous transplants of an ovary and testis in the same castrated infantile animal. Such procedures result in the production of somatic hermaphroditism combined with a decided bisexualism of the psychosexual character.

These and similar observations definitely point to the interstitial cells of the testis as responsible for the deliverance into the blood stream of properties which bring about the proper establishment of the secondary internal generative organs, and indicate that the sexually indifferent somatoplasm is influenced to form sex characteristics in response to the type of the gonadal hormone acting upon it.

At puberty modifications of bodily structure occur, which result in the establishment of the secondary sexual characters. This time, therefore, may be known as the Secondary Differentiated Stage. The advent of this period is ushered in by an enormous proliferation and activity of the interstitial cells, and ripening of the germ cells (Tandler, Allen, Whitehead, and Marshall). Sex and sex characters are fully established and the active sexual life begins. It is true that nothing new somatically is added to the individual at puberty; however, we

must consider this period as a time of sex differentiation associated with growth because the male, in addition to growth and the appearance of hairs at the pubes and axillæ, which is common to both sexes, deviates materally from the course of female specialization. The voice changes, new psychic states appear, and the body as a whole assumes the masculine character.

2. Influence of the Internal Secretion of the Testes upon the Established Sexual Organs.—*Significance of Interstitial Cells.*—Sufficient data have not been put forth to warrant any definite statement relative to the influence of the gonadal hormone upon the germ tissues. Development of these without the interstitial cells is not known to occur in the mammalian male. However, cases of congenital anorchidism, of which eight appear in the literature, demonstrate many of the characters of sex. The case of a young adult described by Wildholz showed a great development of the subcutaneous fat. The "secondary sexual characters" were not present; the penis had the dimensions of that of a lad of six years, the prostate was absent, and radiograms of the hand showed detached epiphyses. "Masculinized" female guinea pigs which have been operated upon some years previously, demonstrate a growth of skin resembling a male preputum at the urethric tubercle (Lipschütz). When this is retracted there appear two excrescences, the corpora cavernosa penis, which represents the modified corpora cavernosa clitoridis. The entire organ gives the impression of a hypospadic penis. In addition to these changes there appear two spikes similar in nature to those in the normal male. As a rule, the penis of eunuchs remains normal, hence its amputation in those engaged as harem guards. However, the penis fails to develop properly in the man if castration is performed prior to the advent of puberty (Tandler and Gross). Castration of the adult does not appear to alter to any marked degree the previously established generative organs and secondary sex characters, but atrophic genital organs are greatly benefited by testicular transplants. For instance, Morris (*b*) reports that the implantation of gonadal tissue into a man resulted in the enlargement of an exceedingly atrophic testis. The epididymis and spermatic cord assumed larger proportions, and the penis increased in size, the skin covering it became smooth, and morning erections occurred. An examination of the growing testis made during a second operation revealed an organ of firm consistence and with normal coverings.

Relation of the Testes to the Prostate.—The prostate gland in man and in animals remains of small size until the period of puberty. In animals it undergoes definite cyclic changes which are closely associated with changes in the functional activity of the testes. During the quiescent stage the prostate is composed of a few tubules lined with small, flattened epithelial cells which at times are incapable of secretion. At the approach of the breeding season the tubules grow much larger and the epithelial

cells become columnar. During rut the gland is a mass of tortuous tubules, and is many times larger than during the quiescent period.

Removal of the prostate gland of white rats prevents the successful fertilization of the female although the ability and desire to copulate is not interfered with (Steinach). On the other hand, rats deprived of their testes at the age of four to six weeks show marked atrophy of the prostate. Castration not only inhibits prostatic development, but also leads to involution of the fully formed organ (Walker, Athansow).

The prostate in man normally undergoes atrophy in old age, becoming transformed, after a few years, into a mass of fibrous tissue containing a small number of scattered muscle fibers in a state of degeneration (Deaver and Ashhurst). Similar results follow castration (Griffiths, Wallace and G. Walker). On the other hand, alterations do not occur in the prostate following vasectomy or unilateral castration and vasectomy of the remaining gland (Shattock and Seligmann). The prostate in subjects demonstrating complete atrophy of the testes does not increase in size at the onset of puberty; the fibrous tissue is increased, the glandular tubules do not fully develop and the smooth muscle fibers are reduced in number (Eccles). Cryptorchids with functional interstitial cells show no alterations in the prostate (Hanes, Eccles).

Some general enlargement or hypertrophy of the prostate gland is more often seen than atrophy in men of advanced years. That such a condition is not normal is clear from the fact that some diminution in size occurs in all other generative organs as the sexual life draws to a close, much in the same manner that the generative organs of those animals that have a rutting season decrease in size when that season is passed (Deaver and Ashhurst). Observation available indicate that hypertrophy of the prostate in senile individuals results because of an overproduction of the testicular hormone in combination with a reduced external secretion. If such is true, the total suppression of the testis should lead to involution of the enlarged prostate, a result which is not obtainable by the suppression of the seminal secretion alone (Mieremet). As a matter of fact castration has been advocated and performed as a curative measure in the treatment of prostatic hypertrophy (Harrison, White). However, Remete contends that only normal prostates undergo atrophic changes as a result of castration; the more hypertrophy a prostate shows the less likely is castration to produce any beneficial effects upon it. Dogs are prone to enlargement of the prostate, and they are the only domestic animal which have an infectious urethritis. In other animals castration invariably causes prostatic atrophy, but in dogs it often fails to produce any appreciable influence (Ciechanowski).

The administration of testicular extracts, at times, appears to exert a beneficial effect upon the prostate following removal of the testes (Walker (*a*), Rohleder). Testicular transplants also are sufficient to prevent

prostatic atrophy and even to bring about a regeneration of lost function.

Relation of the Testes to the Seminal Vesicles.—Complete castration during the period of rut prevents the seasonal development of the seminal vesicles, or, if such development has already begun, arrests its further progress. Unilateral castration, however, does not inhibit the growth of the accessory genital glands and has no effect on the symmetrical arrangement of these organs (Marshall).

Accessory Glandular Structures — Occurrence and Function.—In many animals there are accessory glandular structures, perineal, inguinal and preputal glands, which may be considered secondary sex characters inasmuch as they serve as means of attraction between the sexes during the mating season. These glands, as a rule, form secretions of a musky odor, usually peculiar to the male, and often only during the rutting season.

3. Influence of the Internal Secretion of the Testes upon Nervous Structures and Their Functions.—Those structural alterations and manifestations of new functions common at the period of puberty are closely associated with manifestations of new emotional, psychic, and nervous activity. The great structural alterations occurring at this period necessarily throw new work upon the nervous system. The awkwardness of the *storm and stress period,* also the psychic unrest, are probably due more to bodily changes than to any very definite alterations in the nervous system itself or its power to conduct impulses. Such structural changes associated with the assumption of new functions by certain tissues results in a stream of nervous impulses not previously experienced. The individual, because of these conditions, is compelled to reinstate nervous equilibrium and become accustomed to the stream of new impulses, that is, he must form new *"habits of acceptance,"* and establish new nervous reactions (Wheelon). At puberty inactive and dormant nerve centers acquire specific sensibility. This is especially true in relation to the nervous mechanisms concerned in the performance of the sexual act. The cerebral cortex is also affected, as is evident by the appearance of sexual desire and changes of disposition.

Nervous Activity and the Breeding Season.—During the breeding season most animals demonstrate markedly increased vitality. Thus, the bull fur-seal, at the beginning of the breeding season, is in a state of perfect development and shows great nervous activity. At the end of this time, on account of abstinence from food, the strain of battle and the maintenance of the "harem," he becomes reduced to a state of extreme emaciation. The migratory impulses of birds and the instincts of courtship, mating and caring for the young, are closely associated with the periodic growth of the sexual organs. The antics, rapid flights, and display of feathers by birds may not be executed to attract the mate, nevertheless their appearance at this particular season indicates that the internal

impulses to exertion are dependent upon the active phase of the sexual cycle. Stags are in a state of constant sexual excitement during the rutting period and fight one another for the possession of the hinds. At the termination of the season the sexual excitement and fighting ceases and the stags once more herd together peaceably and apart from the females, the antlers are shed and the sexual cycle enters upon its quiescent phase. The functioning of scent glands is also closely associated with the cyclic increase in nervous activity. Although these glands are present throughout the year, the stimulus to activity apparently is wanting save during the breeding season.

In cold-blooded animals there is a periodicity in the occurrence of reflex responses. Thus in the heart of frogs, newts, salamanders and eels vagus inhibition is markedly diminished or absent at times roughly corresponding to the periods of sexual activity (McLean). The male frog, immediately following hibernation and at a time of great emaciation and poor reflex coördination, demonstrates a perfect "embracing reflex." This reflex, maintained throughout the spawning season, is responsible for the posture during the act of copulation. It is elicited by stimuli applied to the skin of the chest and is restricted to a small group of muscles in the fore limbs. The embracing reflex is entirely spinal, as may be shown by stimulation of the chest skin of the isolated segment of the fore limbs. Removal of the testes of the frog results in the loss of reflex sensibility and failure of development of certain secondary characters of sex during the breeding season. Testicular transplants in such frogs are sufficient to establish these seasonal changes, hence the testicular substance either acts directly upon the nerves or upon the muscles supplied by certain of them. Section of the nerves in one fore-arm of the frog prevents seasonal changes in that arm; however, the normal arm develops characteristically. Such observations led Nussbaum to the belief that the castration of the gonads stimulates only certain nerve structures. The error of this conclusion was soon shown to lie in the arrest of motility and sensibility of denervated parts (Pflüger). In spite of this criticism, such observations are of special interest because they indicate that the development of certain seasonal changes are dependent not only upon the elaboration of an internal secretion by the testes, but also upon the presence of a normally functioning nervous apparatus.

Dispositional Characteristics and the Testes.—The quiet and rather phlegmatic temperament of castrated individuals is characteristic. It is reported that the eunuchs of Constantinople are avaricious, illogical, obstinate, possess little judgment and accept information without proof. As a rule, they are fond of children and animals and are faithful in their affections, but possess little courage (Hikmet and Regnault). Their mentality is often deficient and they are very fanatical. Eunuchs of high intellectual ability, however, are not uncommon. The re-

duction in nervous activity of the gelding and steer is in part explained by the actual alterations occurring in the nervous system following gonadectomy. There is a constant diminution in the weight of the brains of castrated rats, a condition in itself sufficient perhaps to account for dispositional and metabolic alterations. The writer has shown that gonadectomy in adult dogs results in a constant and consistent lowering of the systemic blood pressure reaction to standard doses of nicotin (Fig. 13). Inasmuch as nicotin stimulates the vasomotor apparatus, it may be concluded that castration results in a lowered irritability of the vasomotor apparatus. If such nervous alterations result because of interstitial want, the introduction of normal gonadal tissue should relieve the depressed

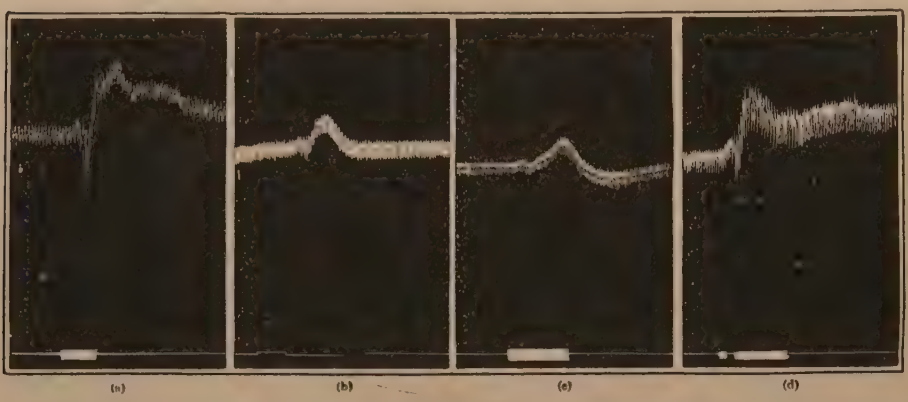

Fig. 13. Vasomotor reactions of dog to 1 c.c. of 1:2,000 solution of nicotin. a, March 1, 1915, before gonadectomy; b, April 20, and c, May 1, 1915, after operation, and d, May 23, 1915, 22 days after the reception of a testicular transplant placed May 1, 1915. Ether anesthesia. (Wheelon and Shipley, 1916, Fig. 3, p. 398.)

function, at least in part. As a matter of fact, the presence of testicular transplants in dogs previously castrated is sufficient partially to reinstate normal vasomotor irritability. Also, the grafting of testicular substance into previously castrated animals and men is of great benefit in reëstablishing sexual powers, libido, and the masculine habits, although spermatogenesis is not established (Lespinasse (*a*) (*b*), Lydston, Morris (*b*), and Lichtenstern).

Somatic and nervous characteristics in animals carrying gonadal tissue of the opposite sex develop, not according to the changes made during the embryological period by reason of the gonads then present, but by reason of gonadal factors derived from the implanted gland. For instance, Steinach, Sand, and Moore have shown that castrated males into which ovaries have been transplanted, develop nervous reflexes normally peculiar to the female. These "feminized-males" show two female reflexes; the *tail erect reflex,* and a *kicking, guarding reflex* to ward off the male before the appearance of heat. Moreover, they are sought by normal males as

though they were females. The "mother instinct" to protect and nurse the young is also noticeable. On the other hand, young female rats have been converted into such apparently mature males that they react psychically as males and imitate the normal male in a very exact way in the act of copulation. Further, Sand has demonstrated that artificially produced hermaphrodites show a mixed psycho-sexual character, that is, they demonstrate activities peculiar to both sexes. From such observations it appears as though the somatoplasm acts simply as an indicator of sex differentiating stimuli.

Erection Centers of the Spinal Cord and the Testes.—The sexual orgasm is usually accompanied by a high degree of mental excitement, although the act of copulation is essentially a reflex action. The nervous centers presiding over this function are located in the lumbar cord (Goltz, Sherrington, Langley, Spina, Budge and Eckhard). The afferent nerves for the *ejaculatory reflex* are the sensory nerves of the penis, especially those of the glans penis. The lumbar center is also open to stimulation from the higher centers, i. e., cerebral or conscious areas (Pussep). However, erection and ejaculation may be induced when all connections with the brain are removed by transection of the spinal cord (Onuf, Goltz).

Early castration results in varying degrees of loss of the power to perform the sexual act. Atrophic changes in the testes of adults also often causes a loss of libido and the power to perform the sexual act. Simpson and Marshall have shown that it is difficult or impossible to induce erection experimentally by stimulation of the nervi erigentes in animals castrated prior to puberty. It is possible that in such animals the musculature of the penis fails to develop sufficiently to admit of erection. On the contrary, if erection is due mainly to an inhibition of the vasomotor nerves to the penis, as is commonly taught, the inhibition of these nerves must in some way depend upon the proper functioning of the interstitial cells. An overaction on the part of the testicular hormone is said to result in an increased libido and power to perform the sexual act (Day).

Genito-Vesicular Reflex and the Testes.—During the ejaculation of semen the capacity of the bladder is increased and its contents prevented from discharging because of the muscular closing of the neck of the bladder and relaxation of the bladder walls. According to Serralach and Pares, similar changes occur in the bladder following the injection of extracts of testicular substance. Extracts of the prostate also cause contraction of the bladder. According to Du Bois and Boulet the intravenous injection of extracts of the normal prostate causes contraction of the bladder. Extracts of hypertrophied human prostate glands have no such effect in most cases, and when they do the result is because of the presence of normal tissue in the hypertrophied gland. According to this finding the retention of urine in subjects of hyper-

trophied prostate is due to the loss of the internal secretion of the gland which acts as an excitant to the vesical muscles. Removal of the growth permits the return of micturition.

Observations on the functions of the prostate lead to a rather complex explanation of the relations existing between the genito-vesicular reflex and the gonadal hormone. As previously shown castration and senility are followed by atrophy of the prostate, whereas hypertrophy occurs with the cessation of the sexual life. Hence, if the prostatic function is conditioned by the proper functioning of the gonadal hormone, and only normal prostates excite the genito-vesicular reflex, it would seem more logical to assume that alterations in this reflex are dependent more upon the internal secretion of the testis than upon an influence mediated by the prostate.

Relation of Spermatic Nerves to the Interstitial Cells.—Section of the nerves contained in the spermatic cord is said to result in the atrophy of the interstitial cells; recent work, however, in no way corroborates such a statement. Resection of the nerves to the testes is followed by degeneration of the seminal epithelium and hypertrophy of the interstitial tissue. Such degenerative changes, according to Kuntz (*a*), are due in all probability to vascular changes resulting because of paralysis of the blood vessels. The blood vessels and all other structures in the testis which contain smooth muscle receive an abundant nerve supply, but such fibers are not distributed to the seminal epithelium or the interstitial cells. If the interstitial cells are dependent upon the reception of nerve impulses for the discharge of their secretory function, it would seem as though the results following testicular transplants and the use of extracts must be due to factors other than the secretion from the interstitial cells.

4. Influence of the Internal Secretion of the Testes upon Growth and Metabolism.—*Metabolism in Different Sexual Stages.*—While it cannot be said that metabolism, as such, is in any way a sexual character, nevertheless the gonadal hormone must be considered as a metabolite which has the power to influence the functions of many tissues. The appearance of the secondary sex characters at the breeding season of animals is indicative of a very rapid metabolism in certain tissues. For instance the stag and American prongbuck develop horns which are shed immediately following the breeding season. Many fishes exhibit marked coloration at this time, a condition indicating active metabolism. The tail of the lyre-bird, which is shed at the close of the mating season not to be renewed again in the same form until the following summer; the brilliant plumage of the breeding drake; the remarkable plate of horn developed in the upper mandible of the pelican during the breeding season, and then shed and the enormous increase in the size of the testes of certain animals are examples of seasonal bodily changes, the existence of which must be connected, either directly or indirectly, with the contemporaneous increase in sexual activity and enhanced vitality. The ap-

pearance of puberty in man also is expressed by an increased vigor which affects both physical and psychical activity. On the other hand, diminution of the functions of the genital glands (hormone) for any cause whatever, is accompanied by senile changes very similar to those resulting from castration. Marked alterations occur in the cuticle and cuticular glands, in the teeth, hair, and neuromuscular system of the aged. General senility also appears prematurely in eunuchs, although the teeth usually remain white and solid.

Alterations in Metabolism Affecting the Testes.—In the testes of old animals and senile men there is a marked and distinctive diminution of the interstitial cells, both in number and size. Evident signs of atrophy are also present, as shown by the profusion of pigment in the cytoplasm and other enclosures. During acute diseases the interstitial cells often become hypertrophied, but during long cachexia they too become atrophic. In experimental intoxication and infection, the interstitial cells hypertrophy at the beginning of the illness but finally become atrophied. Such hypertrophy, according to Ancel and Bouin, Voinov and von Hansemann, is to be regarded as a protective measure on the part of the interstitial glands. As a matter of common observation, hypertrophy and hyperplasia of the interstitial cells are always accompaniments of both imperfect development and secondary atrophy of the seminiferous tissue Eccles, Hanes, Kuntz (*b*)).

Marked alterations occur in the testes following prolonged stravation and improper nourishment. According to Swingle, frog larvæ starved from the time of their emergence from the egg capsule over a period of one hundred days do not grow or pass through the usual metamorphic changes. Microscopic examination of the gonads show that these structures, like somatic development, have been completely inhibited. E. Allen has shown that albino rats fed on a diet deficient in the water-soluble vitamins are sterile; there is complete degeneration of the germ cells. The sustentacular cells alone persist in the tubules, but these show marked degrees of shrinkage of the nuclei. The interstitial tissue, on the other hand, is hypertrophied, a condition analogous to the results following exposure of the testes to the *x*-rays. Similar results have been shown by Portier to occur in the testes of pigeons fed on a devitaminized diet.

Influence of the Testes upon Bone Growth.—The age at which genital maturity takes place is of paramount influence in the growth of the skeleton. Late maturity, like genital hypoplasia, increases height, especially the length of the legs. Premature maturity results in the early closing of the epiphyses and consequently shortening of the lower extremities (Tandler and Gross). In cases of precocious puberty, *pubertas precox virilis,* the acceleration of growth is accompanied by premature closing of the epiphyseal synarthroses (Falta, Strauch, Neurath). Hypoplastic

development of the testes—eunuchoidism—on the other hand, results in protracted epiphyseal separation.

Sellheim (*b*) has shown that castration of cocks has a modifying influence upon the growth of the osseous structures. Changes take place in the skull, pelvis, and bones of the extremities which consist in increased longitudinal growth with retarded ossification of the epiphyseal cartilages. Similar results are also reported for dogs, horses and cattle. Koudelcka observed that the epiphyses of the bull join the shaft by the time the animal is two years old. In bullocks, on the contrary, the processes of endochondral ossification is not completed until the animal is three or four years old. The investigations of Launois and Ray (*b*) (*c*), Tandler and Gross, Gruber, Ecker, Lortet (*c*), Teinturier, Becker, Pittard (*a*), Pirsche, Pelikan, Geddes and others, have shown that castration in man, as in animals, is followed by excessive longitudinal growth of the bones, with a lack of proportion between the length of the extremities and that of the trunk and persistence of the epiphyseal synarthroses beyond the normal age. Following castration endochondral ossification is stimulated and prolonged. However, this does not affect all the cartilages equally and, therefore, the distribution of resulting growth is unequal. Although growth is unequal, it is not fortuitous, but follows a uniform scheme of distribution. The bones most markedly affected are those of the leg, forearm, thigh, arm, pelvic girdle, and lastly the vertebral column. Within the limits of these variations the distribution of osseous alterations is again unequal, the thoracic regional segment being most affected. The skull is altered, with the result that the cranial capacity develops less completely than is normal. The expansion of the antrum of Highmore is retarded as the result of which the face remains narrow. The alveolar processes of the superior maxilla grow out of proportion to the rest of the bone, as also do the mandibular symphysis and coronoid process. Such growth changes are clearly the result of an uncomplicated testicular failure, for they occur in otherwise healthy males if the gonads are removed before the cartilages of the synchondroses are obliterated.

Geddes, who thoroughly reviewed the osseous changes in man following castration, concludes that such changes are the result occasioned by the setting free for general use of foodstuffs which would otherwise have been used to provide for the drain of spermatogenesis. That such is not the case is shown by the fact that the loss of other structures does not result in similar changes. A more logical view is that abnormal bone growth is not due to the fact that the testis is not acting as an organ of reproduction, but to the fact the normal internal secretion from the organ is not available for the controlling of growth of bone in the body (Swale Vincent).

"Feminized" rats and guinea pigs develop osseous structures which resemble the female more closely than the male; the bones are smaller throughout. The reverse is true of "masculinized" animals (Steinach)

(Figs. 2, 3). Hence, the normal growth and development of osseous structures is intimately associated with the elaboration of an internal secretion by the testes.

Fat Metabolism and the Testes.—Gonadectomy is frequently followed by an increased deposition of fat. This is also true in men of advanced age and women after the suppression of the sexual activities. Such depositions of fat are peculiarly localized and to some extent characteristic in each sex. Castrated males, especially men, are sometimes abnormally lean, but the obese type is frequently observed among eunuchs and Scopts (Tandler and Gross (*b*)). In these cases the excessive fat deposition is noted in the mammæ, nates, ventral regions and hips. The true capon is excessively fat; the feeding of testicular substance to such fowls reduces the tendency to obesity.

Sex and Blood Composition.—In insects there exists a sexual difference in the color and protein content of the hemolymph. However, these differences are independent of the gonad, for they remain unaltered in castrated individuals and in those carrying gonads of the opposite sex (Steche). Further, where color differences exist in the blood of the two sexes, it is not due to an enzyme in the male which is destructive to the color found in the female hemolymph; the metachlorophyll cannot be bleached by the addition of male hemolymph (Geyer). The blood of gynandromorphs is of necessity common to the dual sex characters; however, the bisexual characters are maintained. Hence, the soma of such forms is independent of any influence of the gonads. In higher animals such blood pictures are not seen. The addition of blood from the male to blood from the female will not normally cause hemolysis or the throwing down of a precipitate.

The adult male spider-crab contains less fat in the blood and liver than the adult female (Smith). Parasitized males, as previously shown, gradually assume several of the "female" morphological characters; in addition, they take on the type of metabolism of the normal female crab. Similar observations have been reported for fowls; the average total fat in the blood of cocks is less than that of non-laying and laying hens (Riddle). The blood of the human male contains a greater number of red cells, but less fat than that of the female (Gettler and Baker). The rate of metabolism per kgm. of body weight and square meter body surface is slightly greater in men than in women of corresponding weight and height (Benedict and Emmes). There is a difference in the phosphorus content of the blood of the male and female. The values for roosters, non-laying, and laying hens are 6.43, 7.42, and 13.8 respectively (Riddle). Protein metabolism apparently is not affected either by the presence or absence of the testes.

Gaseous Metabolism and the Testes.—So far investigations of the respiratory exchange in relation to the gonads have been very inconclusive

and show no constant change as the result of castration. According to Magnus-Levy and Falk, the gaseous metabolism of boys and girls is not increased during the period of puberty. Lüthje did not find a metabolic reduction in castrated dogs. However, this may be explained by the fact that obesity after castration is by no means invariable, being present in about fifty per cent of the cases. For this reason it has been assumed that the marked diminution in the respiratory exchange observed in some animals following castration is due to a general indolence on the part of the animal. Such results, therefore, as pointed out by von Noorden, should be considered as secondary or indirect, and not due to the removal of oxidizing materials. This criticism finds certain substantiation in the fact that there is a reduction in the irritability of the vasomotor apparatus (Wheelon (*a*)), and a decrease in the weight of the central nervous system (Hatai (*a*)) following removal of the testes. However, according to Löwy and Richter, Pachtner, Murlin and Bailey, castrated dogs do show a reduction in the respiratory metabolism for months following the operation. This fall is in proportion to body weight although a considerable reduction in the total metabolism may occur independent of body weight, the reduction frequently attaining a higher figure as the result of increased adiposity. Angolitti and Kojima have shown that there is an absolute reduction in the production of carbon dioxid following castration, this reduction being greater in the liver than in the muscles. Such findings indicate that a reduction in metabolism is due to diminished oxidization and increased adiposity (Löwy and Richter (*b*), Murlin and Bailey).

Body Temperature and the Testes.—The body temperature is found to be nearly a degree centigrade higher in female than in male rats and guinea pigs. The temperature is reduced following castration of the female. Implantation of testicular material into such animals reduces the temperature still further. On the other hand, castration of the male does not alter body temperature. However, the implantation of an ovary into such a male causes the temperature to rise until it reaches that of the female. Such observations demonstrate a higher rate of oxidation for the female than the male (Lipschütz (*a*)).

5. The Pharmacodynamics of the Testes.—From the time of Brown-Séquard, who popularized organotherapy, to the present day, the deleterious results following the diminution of testicular functions have been combated by the administration of extracts or by the transplantation of gonadal tissue.

Löwy describes a better growth in the wattles and comb of capons fed upon testicular substance than in control birds. More recently Smith and Crocker studied the effects of injections of saline extracts of cocks' testes into the subcutaneous tissues of hens. Such procedures in most cases caused the comb and wattles to enlarge and brighten. The neck feathers became more brilliant, also slight growth and brilliancy of color appeared

in the small feathers at the base of the tail. Egg production diminished and some of the hens tried to cover other hens after the manner of the cock. However, Smith (*d*) has clearly shown that the comb and wattles of both hens and cocks are liable to similar changes in the absence of testicular extracts. It is reported that the skeletal peculiarities resulting from gonadectomy are not observed if young capons are given testicular substance.

Injections of saline extracts of the testis invariably give only a fall in the systemic blood pressure without a preliminary or late rise (Miller and Miller). Such reactions are common to many other tissues of the body, hence no importance can be placed upon them. However, Oliver observed moderate constriction of the vessels of the frog's mesentery following the administration of saline extracts of the testes. The administration of orchitic extracts and the active corpus luteum, according to Jean, results in a diminution of the excretion of phosphoric acid. Lüthje was unable to demonstrate any change in the metabolism of calcium, phosphorus, and magnesium after the administration of testicular extracts. However, the feeding of calcium lactate and lactophosphates in small doses to young chicks causes a marked growth of the body and reproductive organs in the female, but does not affect the male (Pearl). Reach observed the effects of testicular opotherapy on 26 subjects who showed edema and atrophic testes or cryptorchidism. In 14 cases so treated there was complete alleviation of the condition; no results whatever were obtained in the other 12 cases.

The capacity for muscular work apparently is but little affected by testicular extracts. However, according to Zoth and Pregel, the subcutaneous administration of orchitic extracts over a period of weeks during muscular exercise results in an increase of as much as fifty per cent in the muscular performance as shown by ergograph and dumbbell experiments. These results led to the conclusion that the testes tend to reduce nervous and muscular fatigue, but this conclusion is open to criticism, inasmuch as continued exercise in itself is sufficient to increase muscular activity. The testes, however, may exert some definite action on the neuromuscular apparatus, for Rocha has shown that the action of certain drugs varies with the sexual cycle of the animal.

It is true that the exhibition of testicular substance has marked influences upon the body in those suffering because of a gonadal want, but the manner in which this is brought about is not known (Dixon (*a*)(*b*)). The many claims made for Poehl's "spermine," or so-called "active principle of the testis," have not been confirmed. Rosenheim has isolated this same substance, not only from the testes, but also from the pancreas, spleen, brain, cancerous lymphatic tissue, cod's roe, and meat extracts. This material is not present in serum, blood or protein-free milk. According to Dixon and Loisel, the active constituents of testicular extracts are nucleo-

proteins which contain toxic bodies. More recently, the beneficial results following the administration of testicular preparations have been considered due to the presence of nucleoalbum rich in phosphorus, resembling lecithin or glycerophosphates (Sajous). Microscopic studies have definitely shown the presence of fatty particles in the interstitial cells and lymphatics of the testis, the fat content varying with the sexual cycles. Certain investigators, especially Duesberg, contend that these microscopical bodies represent the internal secretion of the testes. However, it is not justifiable at the present time to accept such observations as proving the presence of an internal secretion.

The pharmacodynamics of the testis remains indeterminate. Testicular extracts are complex in nature, and it is at present impossible to obtain pure extracts of the interstitial cells alone. Up to the present time an active principle has not been obtained from the testes which will insure the same reactions as the presence of the testes themselves. However, the results of testicular activity are not pronounced at any one moment; their influence is exerted continuously. Furthermore, the testes are not essential to the life of the individual; their purpose is solely to further the development and maintenance of the sex signs in tissues present. Disturbances of other endocrin glands (Bell) are known to exert marked influences over the metabolism and perhaps, in the absence of the testes, are responsible in great part for the results following removal of the gonadal influence. However, such glands are common to both sexes, while a specific—interstitial—gland is normally confined to one sex.

V. Alterations in Sex and Their Relation to the Testes

1. Assumption of Male Characteristics by the Female.—Darwin records the case of a duck which in her old age assumed the perfect winter and summer plumage of the drake. Baudoin describes a case of "sex inversion" in a bird as the result of diseased ovaries. Castration of the female duck causes it to gradually lose the female characters and assume those of the male.[4] According to Brant, hens invariably acquire cock's plumage after the loss or degeneration of the internal genitals, most commonly because of degeneration of the oviducts. L. Loeb describes the case of a male guinea pig which possessed certain female secondary sexual characters. The testes were small and had not descended. They were made up of interstitial cells and typical tubules which lacked spermatogonia. The interstitial cells were abnormal, containing vacuoles and eosinophilic bodies. The mammary glands were female in character. Old female deer, which have become sterile, incline to antler formation, as do also

[4] For bibliography pertaining to male sex characters in female birds, the reader is referred to the work of Larcher.

females with diseased internal genitals (Rörig). Laignel-Lavastine and Courbon, Hermans, and many others, have described cases of alteration in the sex characters of man following orchitis, trauma and atrophy of the testes. The degree of alteration in such cases is greatest in the young.

Castration of brown Leghorn females, according to Goodale (*c*) results first in the development of male characters, followed by the assumption of the female type of plumage, and still later to the male type. Histological examination of the internal genitalia of castrated subjects showed that remnants of the ovaries left from the operation had not degenerated, and that a new organ had developed. This organ was neither testis nor ovary in character; however, its presence was necessary for the assumption of male plumage. Removal of the testes of birds does not bring about the assumption of female characteristics, but, at most, results in the loss of certain male characters. Hence, as far as birds are concerned, it appears that the female owes her color to the presence of some modifying element which prevents the development of the male color. That is, it prevents the appearance in the female of the male character which is inherited equally by both sexes. The observations of Boring and Morgan are of special interest in this connection. They point out that in the hen there are groups of cells in the ovary (luteal cells) which produce yellow pigment reacting similarly to the luteal pigment of the corpus luteum of the mammal. These cells are absent in the adult male fowl except in case of the Seabright cock, which is feathered like the female (hen-feathered). Castration of these cocks results in the assumption of plumage common to the ordinary male fowl. Hence these special cells through their secretion suppresses in the hen and the Seabright male the characteristic cock feathering.

2. Sex-Intergrades.—Sex, according to the older conception, is an absolute attribute; that is, an organism was supposed to be either male or female except in cases of hermaphroditism. However, recent studies have shown that the blending of "maleness" and "femaleness" (gynandromorphism) in a single individual is not uncommon. Morgan has shown that sex-intergrades are rare, 1:2,200 in the fruit fly, *Drosophilia*. Banta found that sex-intergrades in Cladocera, a small crustacean, when once established tend to produce sex-intergrades indefinitely. A race of Cladocera which for 130 generations had been breeding parthenogenically produced only females. In the 131st generation males and sex-intergrades of many sorts appeared. Among these eight morphological secondary sex characters were recognized. Practically every possible combination of male and female character was seen in this generation of crustaceans. Results of a similar nature have been reported by Goldschmidt.

Sex-intergrades may be established experimentally in animals by the simultaneous implantation of gonadal tissue into previously castrated animals. Sand has shown that the implantation of a gonad of one sex into

the body of an animal of the opposite sex possessing functioning generative organs fails to influence the economy of the receptor (Fig. 14). Castration of the experimental animal—a neutral somatoplasm—is a condition *sine qua non* for the ingrafting and efficiency of the heterological gonad, the transplanted organ perishing if castration is omitted. If the reproductive tissue of the two sexes is simultaneously placed in a neutral animal the interstitial tissue of both sexes will intermingle in their growth and produce hormones (Sand, Steinach and Boruttau). Such dual implanta-

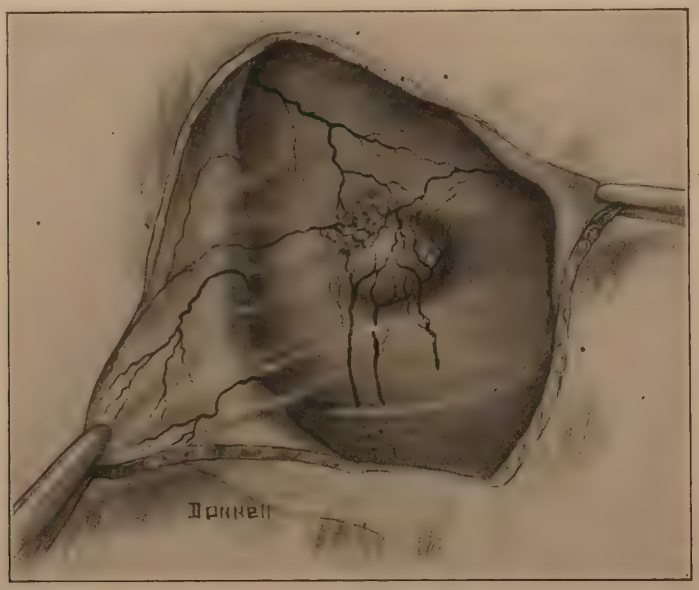

Fig. 14. Drawing to show the degree of encapsulation and peripheral vascularization of a testicular transplant among the shoulder muscles of a normal female white rat 24 weeks after placement. The granular material at the upper border of the transplant represents masses of degenerated spermatic tissue and new fibrous growth. (Original.)

tions into a previously spayed female results in the development of male secondary characters and skeletal and muscular growth comparable to that of the male. Psychically the subject behaves at times as a male and at other times as a female. As a male it will fight off other males and seek and attempt to mate with rutting females. At cyclic intervals it behaves as a female and will be sought and courted by males. At these periods it will not fight males and behaves indifferently toward the females; the mammæ become enlarged. Double implants in males bring about similar results. If, however, male interstitial tissue predominates, male characters will predominate, and *vice versa*. It therefore appears as though the gonadal hormones are not antagonistic (Biedl) but exert their influence in proportion to the degree and quantity of their delivery to the somatoplasm (Sand).

Goldschmidt contends that no animal, including the human, is either purely male or female, but each has the potentialities of both. In the light of modern experimental proof hermaphrodites, pseudohermaphrodites, and many persons considered abnormal should be considered as intergrades, and, therefore, not pathological, but simply natural variations, the result of the chromosome complex and of abnormal internal secretions of the gonads. Goldschmidt inclines to the view that these human sex-intergrades are not degenerates, since 50 per cent of them are found in sound families, but that they are the natural result of crossed matings of people of different genetic constitution. The number of "contrary sexualis" is much greater in these people than where the race is pure. Such observations and conclusions substantiate the belief that hermaphroditism depends not on the presence of male and female generative tissue, but on male and female interstitial cells. Hence, normal sex must be considered the result of complete differentiation of the sex gland primordium into one or the other type of interstitial cells.

VI. Conclusion

1. Purpose of the Testicular Hormone.—Early castration is known to inhibit secondary sex differentiation; however, the rather prevalent belief (Biedl) that a transformation to the heterosexual type follows gonadectomy because of a hermaphroditic origin of sex, is not tenable. The body, or somatoplasm, is sexually neutral, or indifferent, save for the influence of the internal secretion of the gonads, hence a loss of this secretion which normally stimulates certain tissues and depresses others results in a tendency to revert to a neutral or indifferent type, or, to use a phrase of Nöel Paton, to a level of *common hereditary inertia.* That is, those forms of life which possess a sexual dimorphism dependent upon the gonads, tend to return to the common or least differentiated type following removal of the primary sex organs, the results of such operative procedures permitting retrogression depending on whether or not the sexual characters are the result of excitatory or inhibitatory influences exerted by way of the interstitial tissue. Thus, there is a potential difference in the weight of the two sexes which is not related to the influences of the sex glands. The males of many species are invariably heavier than the females (Moore). Castration in the horse does not arrest the development of the withers. The gelding in this respect resembling the stallion rather than the mare in which the withers are placed lower. Further, the voice of eunuchs, although high pitched, is not the result of a feminine type of larynx, but of an infantile larynx grown large, differentiation not having taken place. Eunuchs develop one osseous male characteristic, viz., the margo superciliaris. The hair on the body of eunuchs is scanty; it is

absent about the anus and diminished about the pubes and axillæ. Hair on the face may be well developed in old age, but this is also true of old women. The pelvis also is infantile, but not feminine in type.

Studies on the effects of castration, gonad transplantation, the administration of orchitic extracts and a consideration of pathological conditions of the testes constitute a large body of information which intimately connects sexual phenomena with the internal secretion of the testes. This gonadal hormone has the power to influence the metabolism of many somatic structures. The results as a whole demonstrate that the extent of sexual modification in the experimental animal, in general, is in proportion to the immaturity of the operated or treated animal. In other words, the earlier the internal secretion of the gonad is supplied or withdrawn, the more profound is the sexual modification of the individual. Indeed, pseudohermaphroditism may logically be explained in many cases because of an imbalanced equilibrium between the gonadal influences in the mother and child in utero (Broek).

In conclusion it may be said that *the internal secretion of the testes acts as a differentiating factor sufficiently strong to cause deviation from the common path of somatic growth and to stimulate the development of characters of sex. The withdrawal of this factor permits alterations to occur in the somatoplasm which are proportionate to the degree of establishment and dependence of such characters upon the gonadal influence.*

Pathological Anatomy and Histology of the Testicle . . .

. . . . . *David M. Davis*

Anomalies of Development—Hermaphroditism and Pseudohermaphroditism—Anomalies of Formation—Fusion of the Testes—Multiplicity of the Testes—Absence of Part of the Genital Tract—Anomalies of Growth—Atrophy of the Testicle—Hypertrophy of the Testicle—Anomalies of Migration—Arrested Migration—Aberrant Migration—Anomalies of Position—Degenerative Changes—Ectopic Testes—Degenerations Secondary to Changes in Other Endocrine Glands—Senility—Pressure—Toxic—Pigmentation—Amyloid—Gout—Gangrene—Infectious Diseases—Irradiation—Traumatism—Contusions—Wounds—Inflammation—Acute Orchitis—By the Efferent Duct—Hematogenous—Chronic Orchitis—Tumors—Tumors of Adult Tissues—Histoid Tumors—Organoid Tumors—Heterotopic Tumors—Intratesticular Embryoma—Metastatic Tumors—Lymphosarcoma.

Pathological Anatomy and Histology of the Testicle

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BALTIMORE

The classification of lesions of the testicle herein adopted, while not perfect or complete, is at least comprehensive and affords a reasonable structure upon which to build the conceptions of testicular pathology. It is taken largely from the classification of Sebileau and Descomps. The interpretation of tumors and other lesions of the testicle is made difficult by the uncertainty which still exists concerning the origin of the elements of this organ.

Some have questioned the propriety of considering it as a gland, since its secretion consists of formed elements, or its distinctive cells as epithelium, for the same reason. This distinction is, however, academic, and need not interfere in the consideration of the pathological anatomy of the organ. The same may be said of the question whether the interstitial cells are of mesothelial or epithelial origin.

Anomalies

Anomalies of Development

Hermaphroditism and Pseudohermaphroditism.—*True hermaphroditism* is an exceedingly rare condition. Most of the examples of it have been found in the lower animals. It may be bilateral, unilateral, or lateral. In the bilateral form, there are ovaries and testes on both sides; in the unilateral form, ovary and testis on one side, with a single gonad on the other; and in the lateral form, an ovary on one side and a testis on the other. The glands are, almost without exception, markedly altered and without function. The accessory genital organs may show any degree of associated abnormality, usually with characteristics of both sexes. It is said that the bilateral and unilateral forms have never been observed in man.

Pseudohermaphroditism is called masculine or feminine, according to

the type of gonad present. The external genitals are undifferentiated, or show characteristics of the sex opposite to that of the gonad. The tertiary sexual characteristics, such as voice, character, hair development, fat development, etc., commonly approach those of the opposite sex. The gonads are usually without function, and become atrophic, though libido may occur, leading sometimes, where anatomical conditions allow, to relations with persons of both sexes. In masculine pseudohermaphroditism the testes ordinarily remain in the inguinal canal or abdomen, where they undergo the changes usual to cryptorchid testes (see below).

Anomalies of Formation

Fusion of the testes is normal in myxinoids and most of the batrachians. One case has been reported in a human being.

Fig. 1. Interstitial cell hypertrophy, low power. The topography of the hyperplasia, with arrangement in very large groups, can be seen. (After Dürck. See references.)

Multiplicity of the testes has been reported, but the cases are doubtful. Two testes on one side, with none on the other, are described.

Absence of part of the genital tract. No undoubted case of bilateral anorchia has been reported. In so-called unilateral anorchia there is usually a fibrous remnant which probably represents an atrophy. The epididymis, with, usually, a part of the vas deferens, may be missing. The writer observed a rabbit in which epididymis, vas deferens, and seminal vesicle were absent on one side. The corresponding testicle was normal in size and appearance. Complete unilateral absence of testis, epididymis and vas deferens is somewhat more common. In all these anomalies, the left side is about twice as apt to be involved as the right. They are very rare, not more than fifty cases being reported in the literature.

Anomalies of Growth

Atrophy of the Testicle.—This heading includes the early atrophies of the testis, and cannot be sharply defined from the fibrous atrophies following degenerative changes in later life (see below). If the testicle has once begun to develop, and then regresses, one is dealing with an atrophy, rather than with absence, no matter how small a remnant may be left. Atrophies of the fetal period produce a small fibrous nodule, which may descend into the scrotum. They are probably usually due to syphilis. Atrophies of puberty, which are more frequent, produce an infantile, and later a fibrous testicle. They are really a failure of the normal prepubertal evolution. Since the patients are both sterile and impotent, the interstitial cells are also involved. Effeminacy may be observed (Broca, 1877). Some of these cases are undoubtedly due to disease, with hypofunction, of the pituitary body (see below).

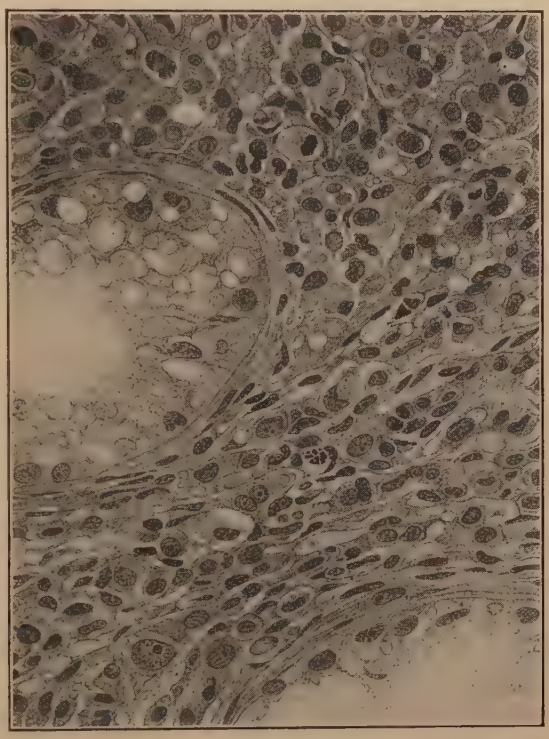


Fig. 2. Interstitial cell hypertrophy, high power. The granular cytoplasm, sometimes filled with small vacuoles, of the interstitial cells, and the almost complete degeneration of spermatogenic elements, can be seen. (After Dürck. See references.)

Hypertrophy of the Testicle.—A certain degree of compensatory hypertrophy may be observed when one testicle is lost in individuals below the age of puberty. In one case, the remaining testicle weighed 60 gms. (Simmonds (*b*), 1910.) There is said to be an increase in the diameter of the tubules. Hypertrophy never occurs after puberty.

Dürck, Pick, and others have described cases in which extensive hyperplasias of the interstitial cells were seen. They have been noted at various ages. The tubules are atrophied, and the interstitial cells comprise most of the tissue, their mass being sufficient to make the atrophic testicle almost as large as, and in one case larger than, the normal. Some of the

cases were in cryptorchids, others in those with scrotal testes. Clinical data are usually lacking, but in one case the man was married, though there is no record of offspring in any case. Neither is there any mention of hypergenitalism. One case in a cryptorchid showed genital hypoplasia. In one case the cells were somewhat irregular and showed mitoses, but though microscopically the organ resembled a tumor, its size had been stationary for years. Apparently the interstitial gland differs from such organs as the thyroid and pituitary, in that simple hyperplasias are not accompanied by signs of hyperfunction.

Anomalies of Migration

Interference with the normal descent of the testes may be said to be due to causes which obstruct it temporarily or permanently, amongst which may be enumerated (1) defects of the mesorchium, (2) paralysis, absence, or faulty insertion of the gubernaculum, (3) narrowness of the vaginal process, or large size of the testicle, (4) shortness of the spermatic cord, (5) rudimentary or obliterated scrotum, and (6) premature obliteration of the inguinal canal. Adhesions due to an early peritonitis have been suggested as the cause of abdominal ectopias, but do not explain most cases. Adhesions in the inguinal canal are usually secondary to trauma or inflammations. Trusses and bandages often cause the testicle to seek abnormal locations after it has emerged from the inguinal canal. The point should be made that delayed descent is frequent, and that ectopia testis is not therefore necessarily a definitive condition. Descent into the scrotum may occur as late as the fifty-eighth year (Sebileau and Descomps).

As to the frequency of this condition, it has been observed in 1.25 per 1000 of conscripts. Among 10,800 soldiers, one bilateral cryptorchid was found. It is about equally common on the two sides. Sixty-seven per cent of all cases of cryptorchidism are said to be inguinal and twelve per cent iliac. The abdominal or infrarenal form is rare.

Other abnormalities often coexist with cryptorchidism, and it is common in pseudohermaphroditism. Normally descended testes may reascend as the result of pressure, trauma, or muscular effort, sometimes reaching the abdomen.

Anomalies of migration may be classified as (1) arrested migration, (2) aberrant migration, (3) intermittent migration.

Arrested Migration.—The testicle may remain in the abdomen, in which case it may be in the lumbar or infrarenal position, or in the iliac position. If it lies in the iliac fossa proper, it is the superior iliac position; if at the internal inguinal ring, the inferior iliac position. In

these cases, the gubernaculum is always hypotrophic, and sometimes absent.

If the testicle descends farther, it produces inguinal ectopia—the common variety. The position may be internal, if the testicle is at the internal ring; interstitial, if it is in the abdominal wall; or external, if it is at the external ring. Since cryptorchidism is the rule in aplasia of the abdominal wall muscles, we may assume that the migration of the testicle is in some way associated with the normal development of the abdominal wall.

If the testicle lies below the external ring, but not in its normal position, the condition is called infra-inguinal ectopia. This is of little importance, since the testes remain normal and often descend later to their normal positions.

Aberrant Migration.—When the testicle seeks an abnormal position, it may be considered that (1) the implantation of the gubernaculum has been faulty, or (2) pressure or trauma have caused the ectopia. The ectopias resulting from aberrant migration may be classified as follows:

Intra-abdominal.

(a) pelvic—in the small pelvis.
(b) deep crural—the testis descends through the femoral ring to lie under the cribiform fascia (like femoral hernia).

Extra-abdominal.

(a) superficial crural—usually caused by pressure on a normally descending testis; fairly common.
(b) cruro-scrotal—the testis lies in the cruro-scrotal fold; rare.
(c) pubo-penile—at the base of the penis, in front of the pubis; rare.
(d) penile—beneath the skin of the penis; very rare.
(e) subcutaneous abdominal—the testis slides out under the skin at varying distances from the external ring; sometimes it reënters the muscles higher up.
(f) perineal—the testis lies beneath the skin of the perineum; eighty-seven cases reported.
(g) transverse—lies in the opposite side of the scrotum; five cases reported.

Intermittent Migration.—Occasionally, the vaginal process remaining patent, the testicle may move up and down between the scrotum and the internal inguinal ring, or even the abdomen, recalling the arrangement in certain animals (rodents). This condition is very rare.

Anomalies of Position

These include the conditions in which the testicle is rotated, inverted, or otherwise changed from the way in which it normally hangs in the scrotum. They are of no interest in connection with endocrinology.

In all ectopias, the testicle may be fixed or mobile, depending on the presence or absence of adhesions. There may be dislocation of the epididymis from the testicle, or prolapse of the vas deferens below the ectopic testicle.

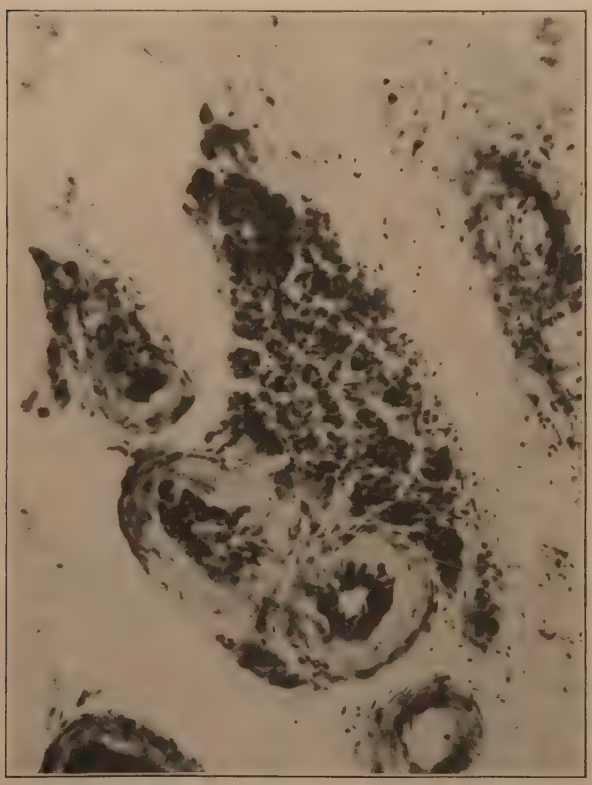


Fig. 3. Section of a cryptorchid testicle, showing atrophic tubules, with diminished epithelium, aspermatogenesis, thickened and hyaline tubular walls, fibrosis of the stroma, and marked hypertrophy of the interstitial cells. X 130. (Brady Urological Institute collection.)

In infants, the ectopic testis is, as a rule, slightly smaller than normal, and shows some increase in connective tissue. No epithelial change is evident. The interstitial cells are normal or increased in number. At the time of puberty, spermatogenesis does not begin. This is an almost universal rule, but in exceptional cases spermatogenesis may be normal, and the individual be fecund. Thus, in a case treated in the Johns Hopkins Hospital, a double cryptorchid had been the father of four children. The testes examined at autopsy appeared normal, with spermatozoa in the tubules. The cause of the usual aspermatogenesis may be the existence of adhesions in the rete region, causing obstruction. Except in these very unusual cases, the spermatogenic cells soon become granular and undergo fatty degeneration, the walls of the tubules thicken and become folded, and finally the epithelial elements disappear, leaving only the fibrotic stroma. The interstitial cells usually persist, and as one would expect, the accessory sexual characteristics are developed, and libido is pres-

ent. A number of observers state that there is regularly a distinct increase in the interstitial cells in cryptorchid testes. Abdominal testicles atrophy earlier than inguinal. It has been suggested that the pathological change in ectopic testes is due to a perivascular interstitial orchitis, since there is a slight round cell infiltration about the vessels. The cause of the change remains in doubt, and degeneration of this kind would naturally be accompanied by some inflammatory reaction. Trauma apparently does not play a part, since abdominal testes atrophy more quickly than inguinal. Obstruction of the efferent ducts, as in epididymitis, ordinarily causes no atrophy of the spermatogenic elements.

In spite of the persistence, at least for a time, of the interstitial cells in ectopic testes, bicryptorchids usually show a deficiency in their accessory sexual characteristics, being often small, adipose and of retarded development. Manifestations of puberty may be absent. In later life they may assume a habitus marking sexual indifference. If descent of the testicles occurs late, a change to the normal male status may take place in a short time. In some exceptional cases, less rare however than those in which testicular atrophy does not occur, sterile bicryptorchids may have male characteristics and practice coitus. In all such cases interstitial cells are found in the atrophic testes. It may be stated, therefore, that there is always a direct relationship between the persisting interstitial cells and the accessory sexual characteristics. It is a rule, but not a general one, that abdominal cryptorchid testes are more likely to lose their interstitial cells than those lying in the inguinal canal.

Experimental studies show that when the vas deferens is ligated in young individuals, the spermatogenic apparatus atrophies, while the interstitial cells persist for a varying time. They may disappear at once, they may remain indefinitely, or they may degenerate at some intermediate period. When double castration is performed before the age of puberty, the individual becomes a eunuch, being sterile and impotent, and showing lack of sex differentiation in the habitus. If, on the contrary, both testes are removed from an adult, the result is more uncertain. He becomes sterile at once, but potency, libido, and the male habitus may persist for a variable time or permanently. In some cases, however, secondary changes appear at once, the voice becoming high and the character effeminate.

Ectopic testes are subject to the same inflammations as normal organs; indeed, it is stated that, for example, in a monocryptorchid who contracts gonorrhea, the retained organ is more apt to become the seat of an epididymitis than the normal one. If the vaginal process remains patent, an epididymitis may set up, by extension, a local or general peritonitis.

It is commonly stated that ectopic testicles are especially apt to become the seat of malignant changes. Bland-Sutton, in England, found that among fifty-seven testicular tumors, forty-eight (eighty-four per cent)

were in ectopic testes, but Schoedel reported the frequency as five in forty-one, and Chevassu (*a*) (*b*) as fifteen in 128; of these fifteen, ten were inguinal and five abdominal. Bulkeley, after a careful study of the literature, concludes that the best statistics show that there is about one abdominal cryptorchid in 800 men, and one malignant abdominal cryptorchid in 60,000 men. Therefore, one in seventy-five of abdominal retained testes becomes malignant. In normal testes, records of hospital patients show one malignant tumor to about 160 males. If the general population were taken, this proportion would be even less. Therefore, while retained testes are at least twice as apt to become malignant as normal testes, it cannot be said that a very large proportion of them do so.

Aside from ectopias, there are cases of congenital azoospermia in apparently normal men.

Degenerative Changes

Degenerative changes may involve the spermatogenic tissue alone or both it and the interstitial cells.

Ectopic Testes.—The degeneration of ectopic testes has been discussed above.

Degenerations Secondary to Changes in Other Endocrine Glands.—Fröhlich (1901) first described the genital aplasia in acromegaly. Cushing and Goetsch placed our understanding of this syndrome on a firm experimental basis. Insufficiency of the anterior lobe of the pituitary body, from any cause, produces an atrophy of the testicle involving all its elements and followed by sterility, impotence, and the constitutional changes associated with genital insufficiency. The testis become small and fibrous. Hyperpituitarism, occurring in hyperplasias or early tumors of the pituitary, or caused by feeding the powdered gland (anterior lobe), produces sexual precocity, with hypertrophy and hyperactivity of all the elements of the testis, which can be observed microscopically. The hyperplasia of the interstitial cells, while definite, is not proportional to that of the spermatogenic elements. Extracts of the posterior lobe of the hypophysis, and of the ovary, have a retarding effect on the testis, with decreased development of all testicular elements, and subnormal spermatogenic activity. Genital precocity and hyperplasia have also been observed in tumors of the adrenal. Endocrine syndromes are undoubtedly responsible for many of the so-called idiopathic testicular atrophies.

Senility.—In old age, the testis may become smaller, softer and browner, or harder and more fibrous. The first form is considered normal, and in it, while the tubules are narrowed and somewhat thickened, spermatogenesis persists. In the second form, there is an overgrowth of fibrous tissue, the epithelial elements disappear, the Sertoli cells persisting

longest, and spermatogenesis ceases. Normally, potency should last until the seventieth or eightieth year, sometimes longer. The interstitial cells survive the spermatogenic elements, and therefore libido often outlasts fecundity. In old testicles small scars are often seen, due to obliteration of some of the tubules, and are said to occur more frequently in arteriosclerotics.

Pressure.—Atrophic changes from pressure in hydrocele, hernia, elephantiasis, etc., do not occur or are extraordinarily slight.

Postoperative.—Following certain operative procedures, especially those for hernia and varicocele, the testicle may undergo fibrous atrophy. This is due to interference with the circulation of the testicle.

Toxic.—Degenerations occur as a result of toxic substances, such as alcohol, lead, etc. The changes produced by alcohol are entirely microscopic, and consist of thickening, hyaline degeneration, and narrowing of the tubules, with a metaplasia of the epithelium to a cylindrical form, and in advanced cases, cessation of spermatogenesis. The interstitial cells survive. Extensive destruction of liver tissue causes alterations in the testicle, apparently toxic in nature.

Pigmentation.—Pigments, like those found elsewhere in the body, are deposited in the testicle in bronze diabetes. Senile testes contain a brown pigment.

Amyloid.—Amyloid is found in the testicular vessels in amyloidosis.

Gout.—In very rare cases of gout, deposits of sodium biurate are found in the testis.

Infarction.—Infarcts of the testicle are rare, but may occur as a result of thrombosis or embolism.

Gangrene.—Gangrene of the testicle may occur as a result of traumatism or of torsion of the spermatic cord.

Infectious Diseases.—Degenerations of the testicle occur in various infectious diseases, but they are treated under inflammations, since a meticulous distinction is impossible.

Irradiation.—When the testicle is subjected to prolonged action of *x*-rays, a degeneration of the spermatogenic elements occurs, commencing with the least differentiated cells (spermatogonia) and involving later the spermatids, spermatocytes, and spermatozoa. Therefore, cycles already under way at the beginning of the exposure are completed, and sterility appears slowly, but is eventually complete. The tubules are lined with Sertoli cells and a few undifferentiated germ cells. Ordinarily, the interstitial cells are not affected, but if the exposure is very prolonged, they too may succumb, and the testicle undergo fibrous atrophy. If the exposure has not been too long continued, its cessation is followed by a very slow return of the spermatogenic function to normal. Radium emanations are also capable of causing sterility.

Traumatism

Contusions.—Simple contusions of the testicle result in edema and punctate hemorrhage, with resulting fibrous change of greater or less extent. Extensive hemorrhages do not, as a rule, occur. Very severe contusions may result in an induration or fibrous atrophy, or rarely may suppurate. The latter alternative is usually the result of tuberculosis latent at the time of injury. In the most severe form of contusion, the tunica albuginea is ruptured, usually with formation of a fungus testis, and destruction of the organ.

Wounds.—Wounds of the testicles are usually perforating. Their pathology is of little interest in relation to endocrinology, except as it may result in destruction, partial or complete, of testicular tissue.

Inflammation

The division of inflammations into acute and chronic must be more or less empirical. Inflammations usually acute may become chronic. Fibrosis testis has not been considered as a separate subject, but it is discussed under various diseases which may cause it.

Acute Orchitis

By the Efferent Duct.—*Gonorrheal.*—Gonorrheal infections are the most frequent and important of those affecting the testicle, yet they usually involve it only in an indirect manner. Following a gonorrheal urethritis, the infection reaches the epididymis, either by extension through the vas deferens, or by the carriage of infectious matter through it by antiperistalsis. An acute inflammation occurs in the epididymis, which may resolve or suppurate. If it suppurates, the abscess or abscesses may open to the outside, or into the tunica vaginalis, or the pus may be encapsulated. In any case, however, scar formation occurs, with atresia of the duct of the epididymis. This is almost without exception, since the duct is single and very convoluted. As a result, no spermatozoa can leave the testis. When obstruction occurs from this cause, there is, strangely enough, no ill effect on the testicle, except in very rare instances. The epithelium is not degenerated, spermatogenesis apparently continues, perhaps at a reduced rate, and the interstitial cells are unharmed. The individual is therefore sterile if the lesion is bilateral, but suffers no other inconvenience. If it is possible to relieve the stricture at a later date, fecundity is usually at once restored. Chevassu reports a

case in which healthy spermatozoa were recovered from a testicle which had been thus obstructed for thirteen years.

Direct extension of the gonorrheal process to the testicle is very rare. When it occurs, it usually involves only those portions of the organ nearest the epididymis, and seldom affects the whole organ.

Non-gonorrheal.—Epididymitis may occur in the same fashion as above with the colon bacillus, staphylococcus, etc., as causative agents. It is usually a secondary invasion of a gonococcal process, or the sequel of some trauma or operative procedure in the neighborhood of the ejaculatory ducts or seminal vesicles. Its clinical course and pathological features are like those of gonorrheal epididymitis.

Fig. 4. Acute pyogenic inflammation of the testicle, low power. The diffuse polymorphonuclear infiltration of all elements, with epithelial degeneration, and fibrosis of the tubular walls, are seen. X 80. (Brady Urological Institute collection.)

When any pyogenic organism causes an acute inflammation of the testicle proper, there is a diffuse polymorphonuclear infiltration of the tissue, with edema and congestion. Whether the infection is by way of the ducts or is hematogenous, the tubules are filled with pus and appear on the cut surface as yellow dots. The epithelium is degenerated and desquamated. The condition may resolve with scar formation, or abscesses may appear. In the latter case, perforation may occur, into the sac of the tunica vaginalis, with periorchitis, or externally, with fistula formation and often fungus testis. The testicle may be completely destroyed, but, if only a portion has been involved, the remainder retains its function. The interstitial cells persist, and if the exit is not obstructed, spermatogenesis will go on.

Hematogenous.—*Mumps.*—An orchitis occurs in one case in three of

mumps, according to military statistics, and in one case in five, according to observers in civilian practice. In certain epidemics, all cases have shown orchitic involvement. The condition is usually unilateral. The testis swells, and there is an epithelial necrosis of the tubules, with degeneration of the inner layers of the coat, whereby they are obliterated. This leads, in bilateral cases, to sterility. The interstitial cells are involved, and in bilateral cases occurring before puberty, there may be eunuchism.

Fig. 5. Acute pyogenic inflammation of the testicle, high power. The same specimen as Fig. 4. X 320. (Brady Urological Institute collection.)

Orchitis may occur without parotitis. The end result in about one-third of the cases, which are most severe, is a fibrous atrophy at the end of several months. The rest recover at least partially. It is stated that late restitution of an atrophic testicle may occur, but this is doubtful.

Variola. — Orchitis occurs in 60-85 per cent of cases of smallpox, a greater percentage than in any other disease. Authorities consider it as a regular manifestation of this disease. The lesion consists of a round and plasma cell infiltration, diffuse or nodular, of the stroma, with vasodilatation, hemorrhage, and epithelial degeneration of the tubules. It is usually benign, leading to complete restitution, but may go on to suppuration or atrophy.

Typhoid Fever.—Orchitis is rather rare in typhoid, sixty-five cases having been reported. It usually occurs at the beginning of convalescence, may recur, and is generally benign, but may lead to suppuration or atrophy.

Scarlatina.—Orchitis is rare. A few cases, not beyond doubt, have been reported.

Influenza and Pneumonia.—A few cases of orchitis complicating

grippe have been reported. Wolbach reports an apparently toxic lesion, with epithelial degeneration and fibrosis, in influenza. Mills describes a lesion consisting of aspermatogenesis, epithelial degeneration, giant cell formation, and slight fibrosis occurring regularly in autopsies of streptococcus and pneumococcus pneumonias. It is apparently entirely benign in those cases which recover.

Rheumatic Fever.—A few doubtful cases of orchitis are reported.

Pyemia.—Metastatic infections with staphylococcus, streptococcus, etc., occur in pyemias and in localized infections with bacteriemia. The pathological picture is described above.

Meningitis.—A few cases of orchitis are reported.

Malta Fever.—Several cases of orchitis are reported.

Vaccinia.—A few doubtful cases of orchitis are reported.

Pyocyaneus.—One case has been reported.

Chronic Orchitis

The lesions of the testicle which become chronic are usually hematogenous.

Tuberculosis.—Tuberculosis usually involves the epididymis first, and extends to the testicle. Its spread in the testicle, therefore, is commonly by way of the tubules. Miliary tuberculosis is of course an exception to this rule. The microscopic picture is the familiar one of tuberculosis. The testicle is enlarged and nodular. There may be caseation, with fistula and even fungus formation, or healing with fibrosis and calcification. All testicular elements are equally involved. The affected testicle shows aspermatogenesis, but if a part is not involved, the interstitial cells there retain their function until they are suppressed by fibrosis. Tubercle bacilli have been found in the apparently healthy testicles of tuberculous patients.

Syphilis.—Syphilis may cause the formation of gummata or of a diffuse fibrosis. Gummata resemble tubercules in their course and results, but are distinguished by a greater vascular involvement, a later disappearance of elastic tissue, and a slighter tendency to necrosis. In syphilitic fibrosis, the entire organ is usually converted into a fibrous mass, with disappearance of all normal elements. It may begin as a hyalinization of the tubules, or as a fibrous overgrowth of the stroma, with round cell infiltration. A surprising feature is the frequent persistence of spermatogenesis and fecundity when only a very small portion of the testicle is not involved. The lesion may be bilateral or unilateral. The diagnosis from other forms of fibrosis may be difficult, and often depends on concomitant manifestations of syphilis elsewhere in the body.

Mycoses.—Sporotrichosis may cause an orchitis, said to resemble that of glanders. Actinomycosis very rarely causes a nodular, tubercle-like

lesion of the testis. Recent investigations have led a number of authors to suspect that mycotic infections are more common than ordinarily assumed. They are usually mistaken for tuberculosis.

Fig. 6. Early tuberculosis of the testicle. The section illustrates the intratubular method of spread, the tubercle developing within the still clearly visible tubular wall. X 150. (Brady Urological Institute collection.)

Glanders. — Glanders is said to affect first the sac of the tunica vaginalis, and secondarily the testis. The lesion is chronic, nodular, and caseating.

Leprosy. — Leprosy causes a productive inflammation, with round and plasma cell infiltration, and early sterility. The bacilli are present in large clumps in the tubules. Simmonds describes a hyperplasia of the interstitial cells.

Filariasis. — A true filarial orchitis may occur, giving rise to an enlarged nodular testis. The lesion is a perilymphatic fibrosis. The testicle is, however, usually not involved in scrotal elephantiasis.

Malarial orchitis has been described, but probably does not occur.

Echinococcus cysts may very rarely involve the testis.

Tumors

Tumors of the testicle offer the greatest difficulties in interpretation. The reader is referred to the detailed literature for extensive discussions of this subject. The classification adopted here is one which gives a fairly satisfactory arrangement of the histological criteria as we understand them at present. Tumors are considered as arising from the tissues normally present in the testis, and from elements foreign thereto. The nature of these foreign elements, which give rise to teratomata and mixed tumors,

is in doubt. Latent twin ova, early and late blastomeres, aberrant primordial differentiated tissues, and germ cells, either of the adult testis or aberrantly placed, developing parthenogenetically, have been suggested. The theory of Ribbert (*b*) that all testicular tumors are teratomata, in most of which all tissues but one have been suppressed, is generally considered too radical.

Tumors of Adult Tissue

Histoid Tumors.—Tumors composed of one type of cell, showing no differentiation into organ-like structures.

Histoid Tumors Peculiar to the Testicle.—(a) Seminoma.—These tumors are the ordinary carcinomata or epitheliomata, the commonest tumors of the testicle. They are made up of cells having large nuclei, scanty,

Fig. 7. Seminoma. The section shows the size and character of the nuclei, the shape and clearness of the cytoplasm, and the round cell infiltration. X 330. (Brady Urological Institute collection.)

delicate protoplasm, and arranged in large alveolar masses. The stroma may be scanty or profuse, and often shows round cell infiltration. The connective tissue reaction may be more abundant than in tumors of other organs. Transition stages are described between these cells and those of the seminal epithelium, from which they are considered to arise. The entire testis is destroyed by the tumor, except occasionally small bits persisting around the periphery. This tumor is malignant, metastasizing fairly early to the regional glands. The seminoma was formerly thought to be a sarcoma, but its epithelial nature is now generally admitted.

(b) Tumors of the Rete (Wolffian epithelium).—Some authors state that these tumors do not exist, but those described by Sakaguchi may well be placed under this head. They resemble closely the above described tumors, except that they contain irregular gland-like spaces lined with columnar epithelium exactly like that of the rete and tubuli recti. Clinically, they are like seminomata.

(c) Tumors of the Interstitial Cells.—Several different tumors have been described as arising from the interstitial cells. The type given by Chevassu, however, is generally accepted. Kaufmann has added other examples. This tumor is ovoid, firm, homogeneous, and of a brown color. The cells are polygonal, often a little separated from one another, and resemble interstitial cells exactly except for the absence of Reinke's crystalloids and the presence of glycogen. They occur in strands rather than alveoli. The tumors show little or no malignancy, and are thought by some not to be true tumors, but merely hyperplasias. Dürck and Pick (*a*) described cases of undoubted interstitial cell hyperplasia. Unfortunately the literature is lacking in any reference to the presence or absence of symptoms of hypergenitalism in these cases.

Common Histoid Tumors.—(a) Fibroma.—Fibromata are rare in the pure state. Histologically, they are like fibromata elsewhere.

(b) Sarcoma.—Sarcoma not arising from teratoma is very rare. The ordinary spindle cell variety is occasionally seen.

Organoid Tumors.—*Adenoma.*—Adenomata are rare. They consist of small nodules, made up of masses of small, highly convoluted tubules filled with epithelial cells, and in some places masses of interstitial cells. They are benign. Tumors arising from the vessels and nerves have not been observed.

Heterotopic Tumors

Intratesticular Embryoma.—*Teratoma.*—Teratomata are the most perfect embryomas. They contain many identifiable tissues, and some assert that they must show derivatives of all three blastodermic layers.

(a) Encysted Teratoma (Dermoid Cyst).—In this form the embryonic tissues are arranged in a cyst, and the two poles of the embryo can sometimes be made out. They are very rare in the male.

(b) Solid Teratoma.—These tumors are a mass of indescribably mixed up tissues of all varieties, leaving no doubt as to the diagnosis.

Mixed Tumor of the Testicle.—This form is even simpler, consisting of many cystic cavities, usually more or less alike, and other tissues, but no sebaceous glands or hair. This rubric includes tumors formerly described as cystoma, cystadenoma, enchondroma, myoma, myxoma, osteoma, etc. They are almost equal to seminomata in frequency.

Degenerated Embryoma.—The above mentioned tumors frequently,

almost, indeed, as a rule, undergo malignant degeneration. This degeneration may take the form of a cylindrical epithelioma, invading the tissues and filling the cysts with papillomatous masses, or large or small round cell or spindle cell sarcoma, or finally of vegetative masses, consisting of a loose edematous stroma surrounded by syncytial masses, exactly like chorionic villi. These masses erode blood vessels, and the tumors are exceedingly malignant, metastasizing early to every part of the body. They are known as chorio-epitheliomata or choriomata. Chevassu has described similar, less well defined structures in tumors in which they form only a small part of the mass, but in which their power to erode blood vessels is apparent. In all malignant degenerations of embryomata, the malignant process soon dominates the clinical and pathological picture.

Tumors of the testicle represent, according to different statistics, one two, or three per cent of all tumors. Chevassu reports, among 128 cases, sixty-two embryomas, fifty-nine seminomas, and seven miscellaneous. They are most frequent in subjects at the period of maximum sexual activity, being rare below eighteen and above fifty. Forty-two cases of malignant tumors in infants have been collected, all varieties being represented. Embryomata are more frequent from eighteen to thirty-five, and seminomata from thirty-five to fifty. In general, therefore, they are more precocious than the tumors of any other organ. The two sides are involved with about equal frequency, and the condition is practically always unilateral. Heredity and traumatism seem to play little part in the causation of these tumors. Their malignancy is indicated by the fact that among cases followed for several years, castration cured one seminoma in three, and one mixed tumor in sixteen. The failure of early recognition is largely responsible for the unfavorable results.

Metastatic Tumors.—Metastases of malignant tumors to the testis are rare. They occur oftenest with melanotic carcinoma, and less frequently with sarcoma and carcinoma.

Lymphosarcoma.—The testicle may be involved in a lymphosarcomatous process.

The Testicle as a Gland of Internal Secretion . . . . . .

. . . . . *V. D. Lespinasse*

The Testes—Embryonal Origin—Growth—Cell Contents—Discussion of Results—Effects of Various Factors on the Testicle—Captivity—Effects of Change in Position—Transplantation of Testicles—Excessive Testicular Hormonic Action—Premature Puberty—Experimental Production of the Eunuchoid State in White Leghorn Cockerels—Testicular Hormonic Deficiencies—Congenital Deficiencies—Acquired Deficiencies—Retarded Puberty—Etiology—Description of Eunuch—Report of Case—Eunuchoidismus—Etiology—Table of Differential Diagnosis of Infantilisms in the Male, Eunuchismus in Its Different Forms, and Eunuchoidismus—Compensatory Action—Satyriasis—Summary.

The Testicle as a Gland of Internal Secretion

V. D. LESPINASSE

CHICAGO

The source of the internal secretion that determines the secondary sexual characteristics must be, in a part at least, from the testicle. In the testicle there are just three possible sources of this secretion: the spermatogenic cells, the Sertoli cells, and the interstitial cells. There is no question but that the source of this hormone is not in the spermatozoa or in the spermatozoa bearing cells because in many conditions these cells are destroyed and there is no change in the secondary sexual characteristics nor in the primary sexual libido. It is not definitely proved that the Sertoli cells do not produce something that is essential to the development of normal sex characteristics, neither is it disproved.

The general consensus of opinion at the present time is that the interstitial cells of the testicle are the important cells in the production of the testicular internal secretion or hormone. This is proven by the fact that these cells are independent relatively of spermatogenesis. Trauma and disease that destroy the spermatogenic cells do not necessarily affect the interstitial cells unless quite severe and in many instances may even increase them. This probably correlates the clinical fact that phthisis patients are exceptionally passionate and cryptorchitic animals always have a normal sexual libido and at times the libido is greater than normal, though they may have no spermatogenic tissues whatsoever.

The Testes

The gross structure of the testes is best seen in a sagittal longitudinal section. Even a low magnification will show that the testes are composed of lobules. These are produced by septa which extend into the substance of the organ and are derived from the investing tunics of the testes and diverge in a radiate manner from the mediastinum testis. The lobules are of pyramidal shape, with their bases directed toward the capsule and their apices toward the mediastinum. They consist principally of the seminiferous tubules, whose transverse, oblique, and longitudinal sections

may be observed in sections of the testis. When isolated, these tubules are seen to begin in the testis as closed canals, which are closely coiled upon each other (convoluted tubules) and describe a tortuous course, until they finally reach the corpus Highmori.

The epithelium of the convoluted seminiferous tubules consists of sustentacular cells (cells or columns of Sertoli) and of spermatogenic elements. The former are high, cylindric structures, the basilar surfaces of which are in contact. They do not form a continuous layer, but their basal processes are interwoven to form a superficial network surrounding the epithelium of the seminiferous tubules. In the meshes of the reticulum are deposited numbers of plate-like cells, which lie in contact with the basement membrane and also represent sustentacular elements.

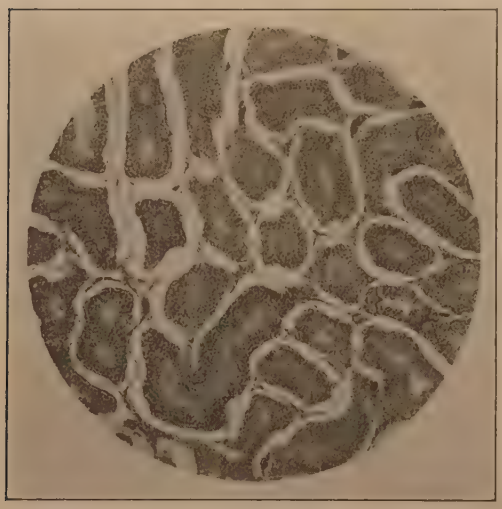


Fig. 1. Photomicrograph of the normal testicle of a dog.

Between the sustentacular cells are found from four to six rows of cells, possessing relatively large nuclei, rich in chromatin, and derived from cells of the deeper strata by mitotic cell division. The epithelium of the convoluted portion of the seminiferous tubules is, therefore, a stratified epithelium. The cells of this epithelium present various peculiarities according to their stage of development, and will not be considered more fully as they have to do with spermatogenesis. Externally, the walls of the convoluted tubules are limited by a single layer or several layers of spindle-shaped, epithelioid cells. A basement membrane is present, but very thin, and in some cases hardly capable of demonstration. The convoluted tubules are separated from each other by a small amount of connective tissue, in which, in addition to the vessels, nerves, etc., are found peculiar groups of large cells containing large nuclei, and known as interstitial cells.

Interstitial cells as seen in a section of the adult testicle appear as a more or less isolated collection of cells lying in the irregular triangular interval between the sections of the seminal tubules. These cells are irregularly quadrangle and are usually molded to fit the irregular space in which they lie. They send out projections which undoubtedly pass between the spermatogenic tubules and anastomose with the projections of the other interstitial cell masses. They are also found between the tubuli

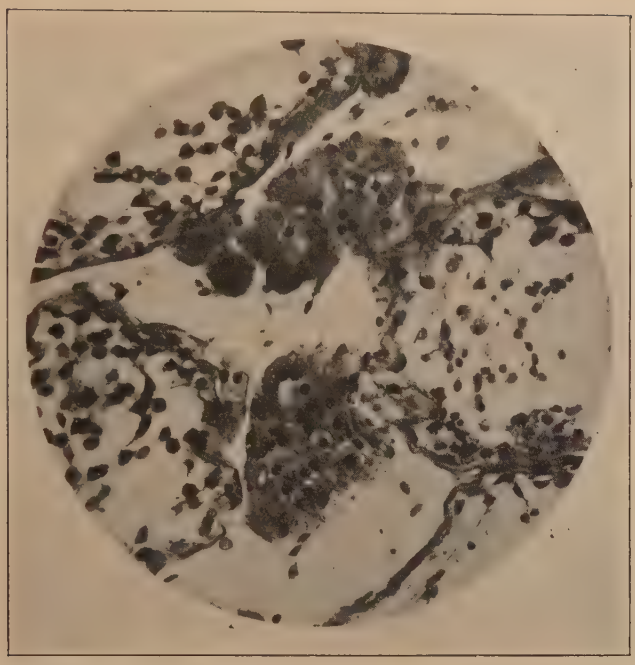


Fig. 2. Magnification 325 shows the interstitial cells as large irregular shaped cells in between the spermatogenic tubercle.

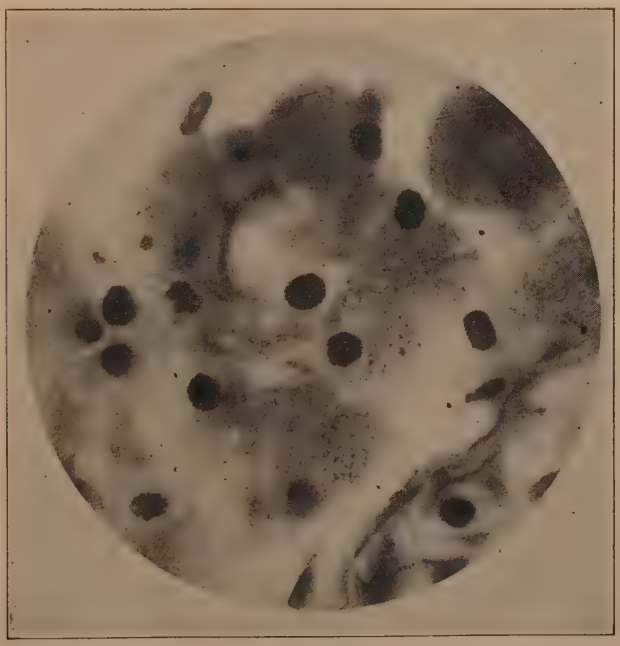


Fig. 3. Picture magnification 1000. This shows the interstitial cells showing the nucleus, vacuoles and granules.

recti along the interlobular septa and immediately beneath the tunica albugenea. They are supported in a meshwork of fibrous reticulum. This meshwork is abundant and tight in some animals and very loose in others.

The relation of the blood supply is naturally intimate because of their location. The arteries coming through to supply the walls of the spermatogenic tubules are in close relation to the cells, but they send out a relatively small number of capillaries to them. The individual cell has an eccentrically placed mass of condensed granular cytoplasm containing the nuclei, while the external portion of the cell is extensively vacuolated.

The extensively vacuolated forms have been considered as old cells, the opposite being youthful forms. The vacuolated spaces may be smooth and regularly circular or they may be long, irregularly shaped with ragged margins.

Embryonal Origin.—It is generally considered that the interstitial cells are formed from Pflüger's cords. They are present very early in the embryonic life of the individual and by some are considered to determine the development of the male sex, as in the female no similar group of cells is observed. Another idea is that the interstitial cells are simply hypodeveloped spermatogenic cells, due either to a general lack of development in the spermatogenic cells as a whole or to pinching off of small fragments of the spermatogenic cells from the general spermatogenic tubule mass to form the interstitial cells. There are three views as to the possible sources of origin for the interstitial cells and each view has its defenders: first, they may be derived from mesenchyme connective tissue cells; secondly, they may develop from Pflüger cords, or thirdly, they may develop from the cells of the spermatogenic tubules.

In the writer's opinion, the interstitial cells are different from, and have no direct origin from, the spermatogenic cells.

The facts to maintain this hypothesis are as follows:

(1) Interstitial cells are formed before the spermatogenic tubules are formed.
(2) They contain granules which are undoubtedly secretion granules.
(3) In many persons with pathological testicles, the individual retains his sexual characteristics and sexual libido even when all the spermatogenic tubules are lacking.

Some have believed that the interstitial cells are ordinary connective tissue cells slightly differentiated. The interstitial cells elaborate granules when the embryo is less than 30 mm. long, whereas spermatogenic tubules only begin to manifest themselves approximately at birth. Consequently, we know that when the spermatogenic tubules have not as yet been developed, the interstitial gland is already actively functioning.

Growth.—The interstitial cells appear when the embryo is 30 mm. long. At about 120 to 150 mm. the semen bearing cords appear and have a

notable increase and the interstitial cells become flattened out, and due to the rapid growth of the spermatogenic cells they are relatively less abundant. In regard to number, the number of interstitial cells is supposed to diminish from embryonic life to birth when there is a cessation and finally just before puberty there is a rapid increase in the number of interstitial cells.

Loisel in some of his work on the testicles of poultry brings out the fact that there are two kinds of interstitial cells, one formed from the connective tissue cells and producing colored pigment and the other a true sexual cell formed from the same embryonic element that forms the spermatogenic tubules and produces a clear secretion. These are the true sexual interstitial cells.

In a typical interstitial cell it will be noted that there is a more or less eccentrically placed mass of condensed granular cytoplasm containing the nucleus; while the peripheral portion of the cell is extensively vacuolated. So marked is this arrangement that one can speak of endoplasm and ectoplasm. By no means all of the cells have this typical structure, but all gradations are found from cells whose bodies are composed entirely of "endoplasm," to those in which it is reduced to a remnant in the immediate vicinity of the nucleus. The vacuolated forms are regarded as old cells by some, the opposite extreme being youthful forms; whereas others think that this appearance is a secretory phenomenon connected with the production of fat. The analogy with what has been observed in various gland cells is certainly very suggestive of secretory function. The vacuoles are not always smooth and regularly circular; frequently they are large, irregularly shaped cavities with more or less ragged margins, doubtless the result of the breaking down of the partitions between adjacent vacuoles.

The nucleus is relatively large, and contains much nuclear sap with a large nucleolus. It is almost always eccentric in position and polychromatic to stains. The finding of mitotic figures in the interstitial cells is rare but some investigators report finding a very few mitotic figures in very fresh material derived from executed criminals. Evidence of karyokinesis is rarely seen in these cells except in the early stages of their embryonic development. It is possible that they multiply by direct division as one occasionally sees two nuclei in a cell and practically never mitoses.

Cell Contents.—*I. Fat.*—As so much importance has been attached by various authors to the existance of fat in these cells, a special study of it should be made. Fat is found in the interstitial cells and in the spermatogenic tubules in all of the common animals except the pig and the oppossum.

The arrangement of the fat in the cells is interesting. It is deposited as small globules which, however, may fuse into larger mulberry-

like masses; but they do not run together into a large sphere, flattening the nucleus out against the cell-wall, as is the case with the typical adipose cell. Rather the arrangement is such as is found in developing fat cells. This characteristic has led some to doubt if the fat is "ordinary fat." The fat in the interstitial cells is for the most part a phosphated lipoid material but cholesterin ester and neutral fat also are probably present.

The fat globules are dissolved by ether, absolute alcohol, xylol, etc., and are stained by both osmic acid and Sudan III—in short, give the usual microchemical reactions employed for the demonstration of fat in other tissues; so that they are undoubtedly ordinary fat.

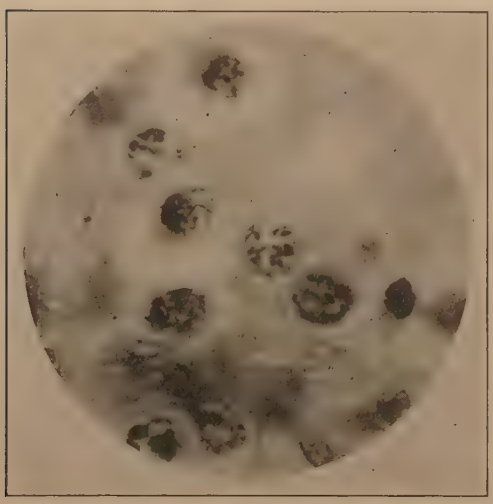


Fig. 4. High power photomicrograph of the nucleus of the interstitial cells to show the chromatin rods of the nucleus.

II. Pigment.—This is not a constant content of the interstitial cells, but is very common in the young testes of chickens. In human material it is rather rare. It is fatty, staining well with Sudan III in frozen sections and faintly even in material that has been treated with alcohol.

III. Crystalloids.—The discovery of crystalloids in the interstitial cells aroused considerable interest as these crystalloids by some are supposed to be the active internal secretion. Crystalloids are present, however, in a very few animals, if, indeed, it is not limited to man.

IV. Specific Granules.—One finds certain definite granules quite constantly present in the mammalian testis, including that of man. To demonstrate them the tissue must be well preserved, and the fixing fluid is of prime importance. Thus, they are quite sensitive to certain acids, fluids containing much acetic acid or potassium bichromate, giving negative results.

Absolute alcohol and 10 per cent formalin give very satisfactory fixation. With Mann's methyl blue-eosin they stain red; they are brought out well by iron hematoxylin; but the most distinctive picture is furnished by staining with Reinke's neutral gentian, as modified by Bensley. With this stain the cytoplasm is colored orange, while chromatin and the granules are stained violet; so that an excellent contrast is obtained between the granules and the cytoplasm in which they are imbedded. In such preparations the majority of the interstitial cells contain definite granules one

or two mikrons in diameter, often in clusters. They lie, for the most part, in the peripheral portions of the cells, but may be found anywhere in the cytoplasm. Each granule is contained in a distinct vacuole, as is evident in very thin sections two or three mikrons thick. It is interesting to note that in the case of cells which contain many fat globules, they and these granules lie in these same vacuoles. These granules are few in the rodents, fairly numerous in the dog and sheep, and abundant in the cat, pig and man. They first appear in the pig embryo of 23 mm., after which time they are regularly present. In the undescended testis of a cryptorchid pig they are very numerous. Hence they are probably not related to spermatogenesis, since in such testis the seminal epithelium is undeveloped or atrophied.

The staining reactions of these granules and their sensitiveness to acetic acid call to mind the zymogen granules of the pancreas. On the other hand, the reaction for prozymogen, which usually can be had in cells which produce zymogen, could not be obtained. Our knowledge of the zymogen is so imperfect that it does not seem safe either to affirm or to deny the zymogenic nature of the granules; but, without any reference to their chemical nature, we may regard them as an internal secretion of the interstitial cells.

Discussion of Results

The various theories as to the function of the interstitial cells are that they act as nurse-cells, passing their fat and pigment through minute canals in the walls of the tubules to be received by the Sertoli cells and there used as pabulum in the formation of spermatozoa. Reinke thinks crystalloids are an internal secretion while others think the fat itself is the internal secretion of the interstitial cells, and is poured into the general circulation through the lymphatics. Loisel has advanced the theory that the interstitial cells manufacture an internal secretion out of their fat, and that this secretion produces the secondary sexual characters of the male.

Effects of Various Factors on the Testicle

I. Captivity.—The phenomena of degeneracy are observed with extreme frequency in the testicles of animals in captivity. All sections of the seminiferous tube undergo various alterations, and can be seen at diverse stages of their degeneration.

The degeneracy is observed as much in quiescent cells as in cells undergoing active karyokinesis.

(A) The quiescent cells present protoplasmic lesions of two very different types; the vitreous degeneracy and the granular transformation.

In the vitreous degeneracy, the cytoplasm is first involved. Later on, the nucleus changes and disappears before the cytoplasm. All varieties of degeneration are observed and they follow one another or sometimes associate with one another to make degenerate, bastard types.

(B) Cells "en mitose" are the seat of many alterations, but these alterations are never observed in the stages anterior to the "plague equatoriale."

Degenerate "mitoses" are for the most part asymmetrical.

Sometimes normal "chromosome," and sometimes those of unusual shape and irregular form, distribute themselves in uneven number in two nucleus threads. At other times these chromosomes do not show

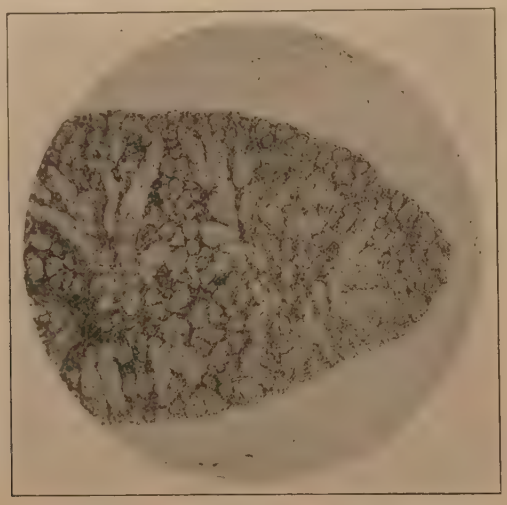


Fig. 5. Low power photomicrograph of a guinea pig testicle whose nerve and blood supply was completely severed but the organ allowed to remain in the scrotum; note that the spermatogenic tubules have disappeared and the organ is a mass of interstitial cells. (A true iso graft.)

any regularity in their distribution. They can be found distributed here and there in the cytoplasm.

The weaving shows us similar anomalies. The vanishing fibers of certain cells thicken on certain others or take wandering directions. The right half of a fusion does not maintain the same shape as the left half. If the upper segment of a fusion is normal, its lower segment may be altogether wanting. Other times, this segment is only truncated; it is terminated on one surface, cut off at right angles; its cut extremity is entirely missing.

One often notes the absence of central corpuscles or their transformation into voluminous bodies of spherical form and acidophile reaction.

It happens sometimes that the nuclei issuing from the "mitose" reform themselves without the cytoplasm participating in the division; a binucleated cell results from this anomaly. Each of these nuclei so

formed can evolve for its own account. For example, one of them can destroy itself by "caryorrhexis," while the other is the seat of an "atypic mitose." The interstitial cells are not involved in these degenerations and the sexual libido is preserved.

In conclusion, the degenerate phenomena which are seen in the testicles of captive animals are not characterized by their nature but by their extreme frequency and their variability; the testicle reacts in a uniform

Fig. 6. What remains of a guinea pig testicle that was replaced in the abdomen after arteries and veins were ligated.

manner to many factors which determine the disappearance of its seminal tissue.

In the ectopic testicle the interstitial cells are more numerous—proportionally—than in the normal testicle. At the same time they are smaller and less compact. Their nucleus presents the same variations of color; their protoplasm has the same general structure as the normal testicle.

The product of secretion revealable by hematoxylin-copper is a little more abundant and presents itself in the form of large peripheral drops.

These cells contain also a small quantity of fatty droplets.

In regard to compensatory hypertrophy of the interstitial cells, the following experiment is of interest:

The deferent canal of a young rabbit's testicle was ligatured and the opposite testicle removed. Six months afterward, a histological study of the testicle was made and it was found that the spermatogenic tubules were degenerated and the interstitial gland was twice its normal volume. We have therefore concluded that the degeneration of the seminal gland was due to the ligature of the deferent canal and the hypertrophy of the interstitial gland to the removing of one of the testicles. This was then a "compensatory hypertrophy."

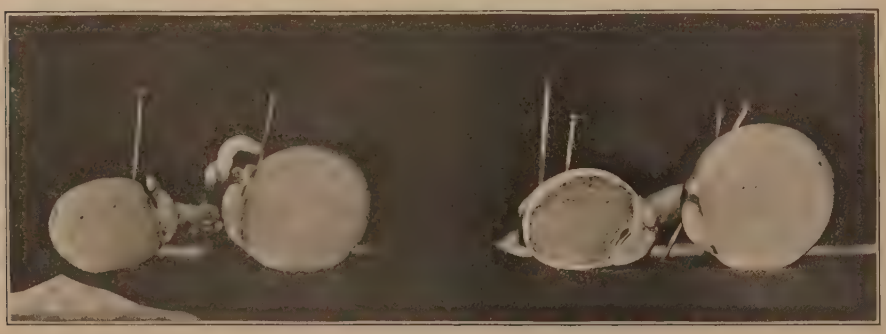


Fig. 7. Testicles from two dogs showing the normal testicle (on the right), the smaller testicle (on the left) having been replaced in the abdomen without interference with its nerve or blood supply two months previously. Note the diminution in size of the abdominally replaced testicle. Photomicrograph of the abdominally replaced testicle is shown in Fig. 12. Compare with Fig. 1.

Another instance to show a possible compensatory hypertrophy is the following:

A pig in whom one testicle had descended and had been removed when the pig was young, while the other testicle remained in the abdomen. This ectopic testicle weighed 180 grammes, while ordinary ectopic pig testicles weigh from about 70 to 90 grammes in cases of double cryptorchidie. This testicle, composed entirely of interstitial cells, as was proved by a microscopic examination, had undergone a *compensatory hypertrophy* and developed the amount of interstitial cell substance normal for two testicles.

One can verify in man an increase in the number of interstitial cells in chronic cachectic conditions; this fact is noted regularly enough in chronic phthisis, cancerous and syphilitic cachexia and in pernicious anemia. In the latter case, the interstitial cells may become as numerous as in the pig.

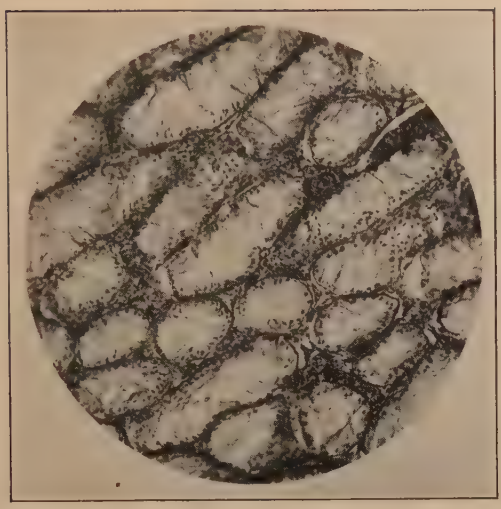


Fig. 8. Normal testicle of a dog that was removed from the scrotum and placed into the abdomen without interference with its nerve and blood supply, but whose vas was ligated. Note the dilatation and the degeneration of the spermatogenic tubules and cells. Note the increase of the interstitial tissue and the presence of a few spermatozoa in the tubules.

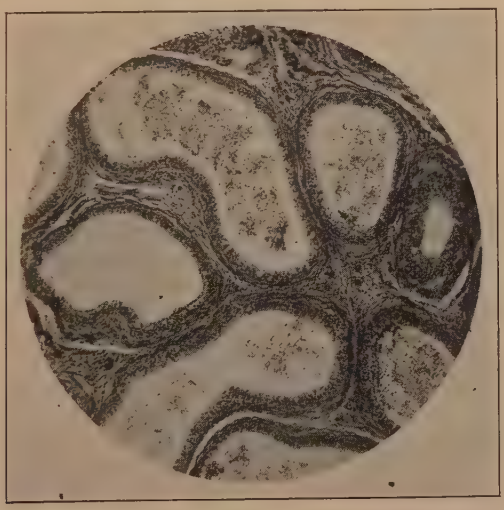


Fig. 9. Epididymis of abdominally replaced testicle shown in Fig. 8. Note the spermatozoa still present in the epididymis tubules.

Effects of Change in Position

The testicle is very sensitive to changes in position. As is well known, the ectopic testicle rarely develops perfect spermatogenesis. Artificially produced ectopic testicles quickly revert to the histologic picture of the

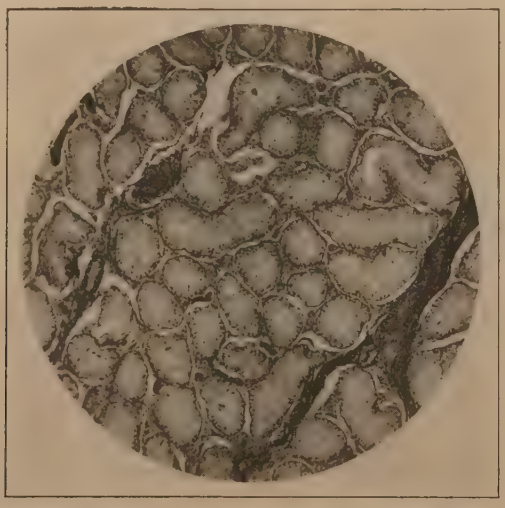


Fig. 10. Dog's testicle replaced in abdomen for 34 days after severing the globus major from the testicle. Note that the cellular elements of the spermatogenic tubules are practically gone but still there are spermatozoa present in the tubules that have not as yet been absorbed.

congenital ectopic testicle. Normal testicles that are placed in the abdomen or in a subcutaneous pocket in the perineum or thigh quickly lose all spermatogenic function followed by an atrophy of the spermatogenic cells, with an increase in the interstitial cell mass.

Alterations in the blood supply, whether ligation of the veins, ligation of the artery, or ligation of both, leaving the testicle in the scrotum, many times produce a complete atrophy and degeneration, and at other times they produce atrophy of the spermatogenic elements only and a preservation of the interstitial cells. This amounts to practically an autograft.

Transplantation of Testicles

In homo transplants, there is in the higher animals an immediate loss of spermatogenic function with complete degeneration of the spermatozoa forming elements. The interstitial cells of the transplant remain and increase in number, retaining their staining properties the same as before the operation. Just how long the interstitial cells live and function after

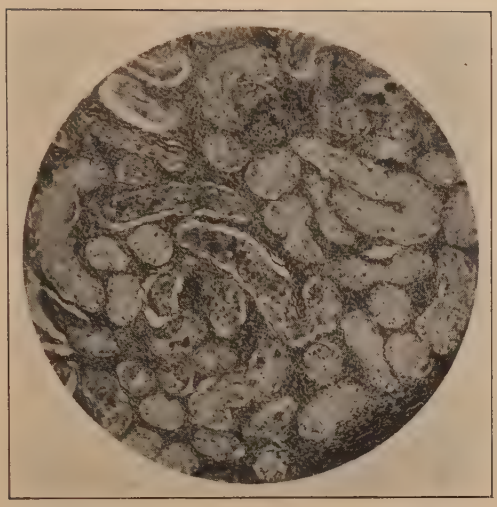


Fig. 11. Dog testicle in abdomen without interference with its nerves or blood supply but with ligation of the vas. Abdominal testicle about one-third size of normal testicle and quite soft. The globus minor of the epididymus was markedly distended.

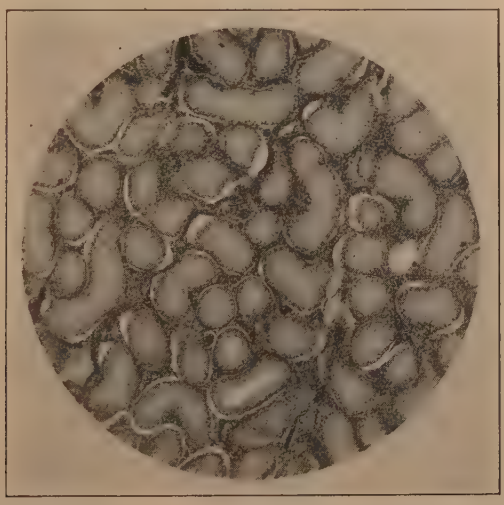


Fig. 12. Photomicrograph of the abdominally replaced testicle of a dog. Note the degeneration of spermatogenic tubules and the increase in the number of interstitial cells. Vas nor epididymus not ligated.

a successful homo transplant is still a question subject to dispute. Personally, I believe that if we really have a successful take that they will live indefinitely. If one does not have a take, the interstitial cells degenerate within a few months. In auto transplants, the same phenomena occur

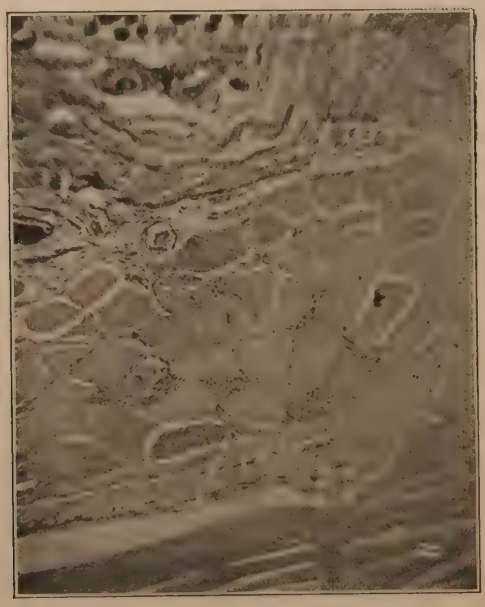


Fig. 13. Low power photomicrograph of the testicle of a dog 3 months after the operation of testicle transplantation; note the degeneration of the spermatogenic tubules and the preservation of the interstitial tissue.

as in the homo transplants. The only difference is that there is a larger percentage of takes.

Excessive Testicular Hormonic Action

Premature Puberty

An early puberty is occasionally observed clinically, coming on at any age from birth to the normal time of development of puberty. Upon analysis, these cases can be classified into four groups; adrenal cortex tumor, testicular tumor, hyperfunction of these structures without tumor, or pineal gland tumor. In the pineal gland tumor cases the patients have in addition to the excessive development of the sex organs, the symptoms due to pressure of the pineal gland tumor upon the brain. From a clinical urological standpoint, these cases have little interest. Adrenal cortex tumor as a cause of precocious puberty is relatively common, more common in girls than in boys. The diagnosis can be made by palpation of the

tumor. These cases are said to have the peculiarity that the testicles do not produce spermatozoa, whereas it is stated that in other types of precocious puberty spermatozoa are produced. This, however, is not absolute, but is simply a presumed fact that should be borne in mind and data obtained upon it whenever circumstances permit. From a scientific point of view, this fact is of great interest as we know that the adrenal cortex is developed from the same embryological structures as the testicular interstitial cells, and histologically the cells of the adrenal cortex have a very similar appearance to the testicular interstitial cells. This fact also bears out the independence of the internal and external secretion of the testicle.

Two very interesting cases showing the relation of the adrenal to early puberty are those of Luiser and Chas. Adams. Luiser's case was that of a boy, five years and seven months old, height 138 cm., who resembled a boy of sixteen to eighteen years of age. All the teeth were erupted except the last four molars. Mons veneris was covered with hair. Penis was 8 to 9 cm. long (in a state of erection 12 to 14 cm.). Testicles were the size of pigeon's eggs.

A long series of measurements made in comparative measurements showed that he exceeded most of the normal measurements of a fifteen year old boy. At autopsy an inoperable tumor the size of a man's head was found attached to the suprarenal capsule. The thymus was not found but the thyroid, pineal and hypophysis were normal in size. This patient shows beautifully the effect of the testicular hormone upon the thymus. Here is a child five years and seven months old. He should have had a sizable thymus but he has none whatever, showing that the thymus is caused to atrophy by excessive function of the sexual hormone.

Chas. Adams' case was that of a boy, normal up to ten years, when puberty set in, after which a great development of muscular strength but little increase in height. At fourteen years and nine months, he had the general appearance of a sturdy little man. For two years his complexion was plethoric and dusky and it was necessary for him to shave daily.

At operation, a large inoperable tumor was found in the region of the left kidney. Patient died one year and five months after the operation.

The autopsy disclosed an enormously enlarged liver, a retroperitoneal tumor that weighed 8½ lbs., adherent to the left kidney but no trace of left adrenal. Right adrenal was normal. The tumor was a malignant hypernephroma, taking origin from the adrenal cortex.

The cases of early puberty due to testicular tumors are interesting. The most striking one in the literature is that of Sacchi. His patient was a boy who when about five years of age noted that the left testicle began to increase in size. At nine years of age the boy had a masculine voice, pubic hair, beard, and a marked development of the penis. The left testicle was enlarged, due to an interstitial neoplasm. The left testicle was removed, and four months afterward the beard disappeared but the hairs

on the upper lip and pubic hair persisted. The voice again became infantile, the penis shrunk and the sexual impulses ceased. In this connection, I would call your attention to my own experimental work upon cockerels, where a marked delay in the development of puberty was obtained by removing portions of the testes. This delay was in direct proportion to the amount of testicle removed.

As an excellent example of a case of probably pure hyperfunction without tumor, we can quote the following, reported by Dr. Robert Stone:

The child is four years old. The boy is remarkably handsome, and when stripped, presents a form of great beauty, which is, in fact, a miniature model of a perfectly developed athlete.

The condition of his muscular and osseous system is extraordinary; the deltoids and other muscles of the arm, forearm, back, and thorax, have the same relations to his height that those of a hard-laboring man would have of a stature of six feet. The muscles of the thigh, gluteal region, and leg, are perhaps better developed than those of the upper extremity, but in nearly the same ratio to the height.

If the child's face is concealed the examiner would declare his figure to be that of a minature man, perfectly developed, and at least 21 years of age.

There seems to be little adipose tissue about him, the muscular prominences being clear and well defined, as if produced by constant exercises or hard labor.

The growth of hair is distinct in the axilla, but by no means so marked as that upon the pubes. As in very robust men, the lumbar and sacral regions are covered with a thick down of dark hair.

His height is now four feet one-quarter inch, and weight nearly seventy pounds; though his mother informs me he weighed seventy-five pounds in the spring, and attributes his diminution to the great number of lumbricoides which infest him.

His penis is that of a well-developed man, measuring in a semi-flaccid state four and a quarter inches in length, and in the state of perfect flaccidity three and a half inches. The prepuce is short, leaving exposed a perfectly formed glans penis. I might state, also, that the papillæ of the corona glandis are in a state of hypertrophy, being distinctly salient, and exquisitely sensitive. The pubes are covered with a luxuriant growth of crisp, curling, dark-brown hair, as found in the adult state. In the scrotum, presenting the appearance of the adult, are two firm, apparently well-developed testicles, perhaps rather under the average size of those organs in the adult. Independently of the penis, the development of these alone would have been decidedly remarkable at that tender age.

The spermatic cords are distinct, and under the finger give the impression of perfect organs.

Carefully examined from the neck down, the appearances are those

of a *perfect man,* whilst the head and face were those of a child. On examining his mouth, it was found to contain only the twenty deciduous teeth of his age, with the exception of the middle incisors of the upper jaw, which were carious to the fangs.

The head was perfectly formed, and bears a proper proportion to the development of the body.

The breadth between the ears across the cerebellum was great; in fact, the anterior development of the cranium was less than the posterior; yet the relation could not be called bad at his early age.

The boy is lively, and seems intelligent, though his speech is imperfect, but he pronounced with facility after his father. He seemed unwilling to talk of own accord before strangers; his father informs me, however, that he is very talkative at home and quite intelligent. His temper is good, and he is almost always in good-humor, but when excited by anger his father alone can manage him, which he does by an old-fashioned, knock-down blow.

His father observed last night, when he slept with him for the first time, a constant erection of the penis, accompanied by a nickering, like an excited stallion, and for these reasons consulted me.

The boy has almost always slept by himself, and on a hard pallet on the floor. His back and shoulders are covered with the *acne simplex* of puberty. He has never been known to attempt masturbation, nor is it known whether he has had sexual relations, although the organ has that appearance. The slightest touch of the penis excites it, and the organ becomes tumid and of the average adult size during the requisite examination.

The voice is that of puberty, and has been so for some time.

He is the seventh child and the third son of his mother; weighed eleven and a half pounds at birth, and fifty-six pounds at three years.

At birth, the glans penis was perfectly uncovered, and the hair on the pubes half an inch long; at one year, things were just as they are now.

Around the thorax under axillæ, he measures	2 ft.	1¼	inches
" " hips " "	1 ft.	2¾	"
" " thigh (middle) " "	1 ft.	2¾	"
Penis in semi-flaccid state " "	4¼ inches		long
" " flaccid state " "	3¾ inches		*full*

in circumference.

Around the arm, below insertion of the deltoid muscle, he measures 8 inches.

Around the neck he measures 1 foot.

Around the head (above ears and over hair) he measures 1 ft. 8 in.

From the meatus auditorius to meatus of opposite side across the occiput, he measures 9¾ inches.

Although his neck is full, there is no remarkable development of the laryngeal cartilages, Pomum Adami.

The next question is in regard to the power of the testicles to secrete. Since I first saw this man-boy, his father has made inquiry as to this fact, and states the following to me as the result:

On the 13th of September, he slept with a near relative, a married lady, the mother of several children. In the middle of the night, she was aroused by finding the boy closely clasped to her back, and her night dress saturated. She thought he had emptied his bladder upon her, but on carrying her hand to the part, she found that it was saturated with a *very different and glutinous material* from that she expected.

I regret that I could not obtain the ejected matter to submit it to a microscopical test. The boy is extremely fond of embracing the opposite sex, though nothing further has been ascertained. In no other of the seven children borne by the same mother has the same condition been observed, and in comparing an elder sister of 10 years I found she was extremely delicate, and only half an inch taller than Theodore.

In terminating this simple statement I may observe that the father presented precocity, having experienced his first sexual indulgence at the age of 8 years. He informed us that between the ages of 10 and 13 years he was a better man than he has ever been since. Delicacy forbids my detailing his prowess at that early age.

A personal case of precocious puberty is that of a boy six years of age with a bilateral cryptorchidism. This boy was of normal size, with face that was inclined to be more that of a little girl than that of a little boy. His psychic reactions, particularly in regard to blushing, were more feminine than masculine. His penis corresponded to that of a normal child at puberty and he had very sparse but long (2 inches) pubic hair, which was quite coarse and perfectly straight. There was no definite information elicited that he had ever attempted sexual relations, but the statement was made that the child was very affectionate and very prone to embrace little girls and women. From these clinical and experimental facts, it is very evident that puberty comes on when the interstitial cells of the testicle produce a predetermined certain amount of secretion, and while in the ordinary process of normal growth this amount of secretion is reached at from 12 to 16 years of age, from a pathological standpoint, it may develop earlier or under other circumstances this amount may be delayed or even never developed.

Testicular Hormonic Deficiencies

I. Congenital deficiencies

1. Pure
   - *(a) Pure early, complete*
   - *(b) Pure later, impotence development, from 30 to 45*
2. Mixed
   - *(a) Pituitary*
   - *(b) Thyroid*
   - *(c) Thymus*
   - *(d) General*

II. Acquired deficiencies

1. Pure
   - *(a) Willfully, Mujerados, and Eunuchs*
   - *(b) Excess normal function*
2. Mixed, congenital, and acquired types in other glands, involving the testicle secondarily.

Experimental Production of the Eunuchoid State in White Leghorn Cockerels

These birds were all the same age and were operated upon at the same age. Photos were taken at practically the same age.

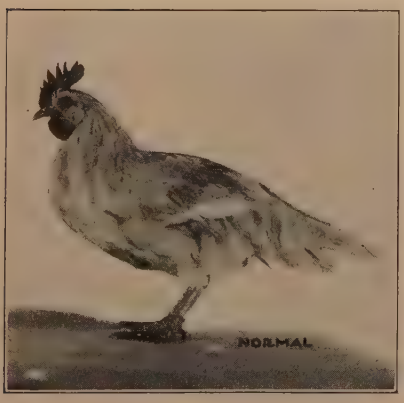


Fig. 14. Note the development of the comb, wattles, head, ear-lobe, and tail in the normal unoperated bird 1.

Fig. 15. Note that in bird 2 which has one-fourth of the testicular volume remaining after operation that the comb, wattles, head, and ear-lobes are much less developed than in bird 1, and that the tail still retains its adolescent characteristics.

Fig. 16. Bird 3, with only one-eighth of the testicular volume remaining, shows a further hypo development of the comb, head, wattles, ear-lobes, and in it you can see the excess development of the tail which is characteristic of the castrated chicken.

Fig. 17. In 4, with only one-sixteenth of the testicular volume present, one can note a further hypo development of comb, wattles, ear-lobe, and head, and a greater development of tail; also increase in size is beginning to show itself.

Figs. 18-19. In 5 and 6, where one thirty-second of the testicular volume was allowed to remain, note the very small head, comb, wattles and ear-lobe, and also note the development of the tail.

Figs. 20-21. In 7, a very small amount of testicle was left, designated as "pinhead" but at autopsy this small piece had sloughed, so this bird is completely castrated, as is also bird 8. Note the increase in size of both as compared to bird 1, practically no comb, small head, and largely developed tail.

Figs. 22-23. Birds 17 and 16 are two Rhode Island Red Cockerels. When one month old, we transplanted into bird 17 two adrenal glands, placing them in the muscles of the breast. Note the precocious sexual development as compared with the normal bird No. 16.

At the time these photos were taken, the normal bird was the only one that was crowing and evincing any sexual libido.

Thus in this series of birds we have produced every state of eunuchism and eunuchoidism and show that the appearance and development of the secondary sexual characteristics are in direct relation to the testicular volume of the individual.

Retarded Puberty

With careful history taking, one can detect many cases of slight retardation of puberty. These patients rarely come to the physician except late in life when their congenitally poorly developed interstitial tissues have broken down earlier than normal, and they come seeking relief for sexual deficiencies. These cases of hormonic deficiency constitute a large percentage of the cases of impotency that one sees clinically. The marked congenital type of sexual deficiency is associated with severe lesions of the pituitary gland, the thyroid, and also is a part of a general bodily deficiency called infantilism.

The commonest and most marked clinical pictures of retarded puberty and hypogenital development in the child are associated with destructive lesions of the anterior lobe of the pituitary. If these destructive lesions occur during infancy they cause cessation of development of the testicle, and genitalia in general, and also the secondary sex characteristics do not develop. If these lesions occur in the individual later in life they will

cause first impotency, then general genital atrophy whose grade will correspond to the amount of destruction of the anterior lobe of the pituitary gland. These cases are easily recognized by the manifold and obvious signs of pituitary gland disease or thyroid disease. Their sexual deficiencies are limited to impotency and sterility as the secondary sex characteristics, bodily configuration and genital development took place earlier in life when the glands were functioning normally. In the late stages of hyperpituitary function when the gland is breaking down and coming into a state of hypofunction, one will have impotency develop, but there will be no change in the bodily secondary sex characteristics, but there may be changes in the sexual psychic sphere.

Fig. 24. Mild grade of eunuchoid who states that he was never sexually vigorous, but broke down completely at the age of forty. Note the feminine distribution of hair, the small testicles, the tendency to fat, but with a masculine build throughout. Normal penis.

Fig. 25. Mild grade of eunuchoid. Note feminine distribution of hair. Normal sized penis. Testicles were normal in size. Breast not developed. No hair on face, peaches and cream complexion. Slight elongation of legs and arms. Weak sexual libida.

The testicle in common with other glands breaks down after excessive function. This condition is excellently shown by the Mujerados. These individuals are developed among the descendants of the Aztecs in Mexico for religious reasons. They are a most excellent example of the breaking down of the testicular function by excessive use or irritation of it. Their production explains many cases of clinical impotence that consult us with histories of marked sexual excesses either alone or in conjunction with physical excesses. They are produced in the following manner:

The man, anywhere from 20 to 35 years of age, is masturbated several times daily, and made to ride horseback constantly. This treatment soon produces an irritable weakness, so that the act of horseback riding produces ejaculations. Gradually as this régime is continued, the testicles atrophy, the penis atrophies, and the pubic hair may or may not disappear. In addition to this, these men's breasts are suckled by babies, and con-

sequently they develop markedly. The bodily shape is not markedly feminine but remains more or less masculine. The scrotum is shrunken and the testicles are very small and not particularly sensitive to pressure. The Mujerados are employed in the occupations usually followed by women.

In mild degree, we meet clinically many of this type of individual. They fall into two groups. First the individual who has a congenitally deficient sexual system and whose sexual organs are used moderately or only slightly in excess. Second, we have the perfectly normal individual who uses or has used his sexual organs markedly in excess. In the first type the general picture is that of a very mild eunuchoid. He usually has little hair on the body; just a few scattered hairs in the median line above the pubic hair line; a slight beard, with a tendency to absence of hair on the cheeks, and the hair to be grouped on the chin and the upper and lower lips. The bodily configuration will show a tendency toward the feminine type with a feminine type of panniculus adiposis.

The testicles are usually small, ranging in typic instances two centimeters in diameter. Good rather marked examples of this condition are Figure 24 and Figure 25. In one of my patients of this type he had an almost feminine distribution of hair with very slight hair in the abdominal midline, and the hair extended down on either side of the scrotum so that when his perineum was inspected his distribution of hair was similar to the distribution of the vulvar hair.

In the second type of case, the secondary sex characteristics are usually very well marked. The individual is distinctly masculine; very hairy; large testicles and penis; deep voiced; heavy beard; thick neck. In other words, he is an exceptionally masculine individual in appearance. Examination is negative in every way except for the complaint of impotency and the testicles are smaller and softer than normal or congenitally small testicle is quite hard. The treatment of this type of patient is purely hygienic, fortified by the administration of endocrin glands. The glands to use are the testicle, the adrenal cortex, and the anterior lobe of the pituitary. In exceptional instances a testicle transplant may be performed upon this type of case.

Etiology

Eunuchs are all due either to accident or design. A congenital process that destroys both testicles is extremely rare. As against this, the classic eunuchoids are practically all congenital, due either to developmental difficulties or to pathological processes which have run their course previous to birth. In the case of acquired eunuchoids, the process is one of breakdown of a normally developed testicle due to excessive function or it is a breakdown from moderate function on a structurally inferior organ.

The classical eunuch is produced by surgical (usually very crude) or accidental complete removal of the testicle while the individual is quite young. Various types of accidents have produced this injury. In addition to the ordinary traumas we have a unique one, namely, the biting off of the scrotum with its contained testicles by animals.

Among the operative methods used to produce eunuchs are the crushing of the testicle, ligature of the scrotum so tight that the scrotum and its contained testes are destroyed and slough, due to lack of blood supply, and lastly the straight surgical removal. Slight traumas to the testicle repeated once to several times daily and continued over a relatively long period of time is one of the older methods of producing eunuchs.

Description of Eunuch

The eunuch is generally taller than the uncastrated man of his race. The skeleton is disproportioned, both upper and lower extremities being longer than would accord with total height. The increased height is found in the lower half of the skeleton, rather than the upper, taking the pubic bone as the diving line.

The skeleton is delicately built. The bones of hands and feet are long and slender. The pelvis usually, but not always, approaches the female type, particularly as shown by its transverse measurements. It is lightly built. The pelvic inlet may be widened while the outlet may retain male form. The upper and lower jaws are powerfully developed, giving a heavy expression to the face. The root of the nose is depressed. The margo supraciliaris is well developed.

The epiphyseal unions remain unossified far beyond the normal period.

The neck is rounded and childlike. The larynx is small. Both the thyroid and cricoid cartilages remain unossified. The prominentia laryngia is absent or shows scarcely a trace. In general the larynx resembles in form and dimensions that of a large child; the characteristics of an adult male are lacking. The voice is that of a boy at the age of the "break," uncertain, wavering, usually shrill and light toned.

The skin of the face is yellowish; that of the trunk, pale, lacking in pigment, soft.

The hair of the head is abundant and soft. It early turns gray. The trunk and legs are free of hair, but there may be a little hair on arms and forearms. A short lanugo takes the place of hair on face and neck, except that there may be single long hairs on outer corner of upper lip and on chin; these never, however, appear underneath chin or on neck; in character and situation they are similar to the hairs that are frequently found on the faces of old women. The eyebrows are well developed, but never show the bushy hairs that are normal in male middle and old age. The

axillary hairs are scarce or absent. The pubic hair absent or limited to the mons veneris, where it has feminine configuration.

The face shows wrinkles even in early life, particularly about the mouth and eyes. In later life it becomes excessively wrinkled.

As regards adiposity, there are two types of eunuchs—the emaciated type and the fat type.

Height and disproportion are more pronounced in the emaciated type; the face has a faded, old-age appearance.

The fat type has a generally bloated, swollen look.

In both types is found the characteristic collection of adipose tissue in certain definite areas, i. e., lower abdomen, hips, nates, breasts, and lateral to the upper eyelids, which last gives a peculiar sleepy expression to the face. In the fat type the fat is distributed all over the body, but in these regions in particular, is excessive.

The musculature in general is weak.

When castration has taken place in early life there is a general underdevelopment of the entire genital apparatus, a standstill at a certain grade of development. Prostate, seminal vesicles and ducts remain in a more or less infantile condition. Penis, if it remains, will resemble that of a young boy.

The functional separation of the urinary and generative apparatuses is clearly seen. While the muscle corpus cavernosum urethræ and the m. bulbocavernosus surrounding the bulbus urethralis have reached a development commensurate with the age of the individual, the muscle corpora cavernosa penis and the m. ischiocavernosus have stayed behind in their development or even fallen a prey to inactivity atrophy.

The vita sexualis may be extinguished, or it may continue in greater or less degree. There may be erection and ejaculation, the former of short duration, the latter watery and thin.

A report by Tandler of one of the scopzi, Jacob, illustrates well the persistency of the sexual libido and ability in the castrated individual:

Jacob is 42 years old, castrated at 21 years of age. Height is 156½ cm., span of arms 163 cm., upper border sym. pubis to floor 78 cm. He is thick set, broad shouldered and well proportioned except for unusually long arms. The hair of the head is fine, thick and brown; the skin of the face is wrinkled and furrowed, and there are some long hairs at the corner of the mouth and on the chin. The axillary hair is scarce; prominentia laryngia scarcely shows. The thyroid cartilage is soft while the thyroid gland is palpable and apparently normal. Crines pubis is limited to mons veneris and ends superiorly in a horizontal line. Hair is very scarce.

The penis development is the same as in a boy of 14 to 16 years old. Below the penis the remains of the scrotum are manifest as a slight prominence of skin, in the center of which is a three rayed white scar. Per rec-

tum: there is a scarcely noticeable prostate; the seminal vesicles are not palpable.

Practiced coitus daily. Erection short duration. Orgasm came quickly, ejaculation sparse, watery and thin. Evidently this man had a compensating function develop from either the pituitary or adrenal cortex that almost completely replaced the testicular hormone.

Report of Case.—A man, aged 38, consulted me in January, 1911, to determine if anything could be done for him to compensate for the loss of both testicles. One testicle which had been retained was removed during a hernia operation; the other had been lost by an accident about two years previous to his consultation with me. He was unable to have intercourse, which was his chief reason for coming to me.

A testicle from a normal man was easily obtained. In fact, I was surprised at the number of testicles that are available for transplantation purpose.

The two patients were anesthetized at the same time, and the recipient prepared as follows: The scrotum was opened high up and a bed prepared in the same way as we prepare the bed for the reception of an undescended testicle. Hemostasis was carried out with great care. Another incision was made over the rectus abdominalis muscle; this incision was carried down through the skin and fascia. The fibers of the rectus muscle were exposed and these fibers separated by opening an artery forceps plunged into the muscle. Hemostasis was carried out and then the testicle to be transplanted was removed. It was immediately stripped of the epididymis, cord and tunica vaginalis, and then sliced transversely to its long axis, these slices being approximately 1 mm. in thickness. The central slice and the one next to it were taken out and placed among the fibers of the rectus muscle. Another slice was placed in the scrotum. The wounds were closed without drainage and healed by first intention throughout.

On the fourth day after the operation the patient had a strong erection accompanied by marked sexual desire. He insisted on leaving the hospital to satisfy this desire. The desire and power of erection continued for five years, since which time I have lost track of him. All eunuchs should have the benefit of a testicular transplant.

Eunuchoidismus

Etiology.—The usual cause of eunuchoidismus is given as congenital. This simply means that there has been for some reason or other a lack of development of the testicular elements to a greater or less degree. To go further, this lack of development may have been simply an embryological omission or a non-development of the formed bud. Many of these cases

may be explained upon simple embryologic maldevelopmental grounds, but it is possible that some of them may be due to a commingling of the maternal and fetal bloods. Dr. Lille in his very excellent work on free martins in cattle has shown that the hypo-developed female is due to the commingling of the two embryonic bloods, and as we know that the interstitial cells of the testicle are laid down much earlier than the corresponding cells in the ovary, and that the hormone from these interstitial cells of the testicles circulates in the blood of the female embryo, thus disorganizing the normal ovarian development and tending to change it to a more or less of a testicular development. May it not be possible that the eunuchoid individual had a direct connection between his fetal blood and his mother's blood so that the strong ovarium hormones from his mother disarranged the normal testicular development and so tended to develop a female type of individual?

Fig. 26. Boy is 19 years old, six feet four inches tall. Testicles are size of a peanut. Penis is about the size of the last joint of the thumb. Bodily configuration decidedly feminine. Note particularly the breast development; the feminine cast of facies; the long legs and long arms.

Fig. 27. Note long arms, feminine distribution of hair. Relatively small penis, moderately sized testicle, breast development, feminine pelvis. Patient married. Has intercourse once a month to once in two months. Ejaculation only few drops, contains lecithin bodies and prostatic bodies but no spermatozoa. Note the careworn expression of face typical of eunuch.

In an acquired eunuchismus or eunuchoidismus we have the following factors in its etiology: testicular trauma, torsions of the cord, inflammatory diseases of the testicle of all sorts, and nerve lesions involving the spermatic plexus, the lumbo-spinal cord, and the cerebellum. The exact effect of these on the individual depends on the age at which they occur and the exact extent of the lesion.

The eunuchoid, as the name implies, has many of the characteristics of the eunuch. He is usually tall, with long legs and long arms, and a relatively short body. The bodily hair distribution is usually feminine; the pubic hair being cut straight across with no abdominal hair, moderate hair in

the axillæ, and a slight beard which develops more on the upper lip and chin than on any other portion of the face. The body configuration may be typically feminine or may grade from this to a normal masculine shape. The penile development is usually below normal, but may be normal. Testicles vary in size from practically nothing to relatively normal, and in location all grades of non-descent are frequently met.

Fig. 28. Typical eunuchoid. Note the feminine distribution of hair, feminine breasts, feminine shaped pelvis and thighs, normal sized penis and very small testicles. Also note the characteristic careworn expression of the face.

Clinically we have the pure eunuchoid or gonadal type, and then we may have the various other types, in which one or more other internal secretion glands are involved, and then the picture is clouded by the changes due to the particular gland involved. The mental attitude of the eunuchoid varies greatly. Some of them are distinctly masculine in their outlook upon life, and others are decidedly feminine, and we find many peculiar mixtures of the different mental sex characteristics in these individuals. Their sexual libido as a rule is below normal. Fig. 27 is that of a Russian Jewish man who stated that he had intercourse approximately once a month. The ejaculation from this individual was very small; simply enough to moisten the inside of the condom. It contained a few lecithin granules and prostatic bodies but no spermatozoa.

The individual depicted in Fig. 26 has testicles about the size of the kernels in a peanut, with a penis in a non-erect state of approximately the size of the last joint of the thumb. He, however, has a very marked libido, practically normal, but as you can see from the picture, his bodily configuration and his breast development are decidedly feminine. He is a boy about 19 years old with six brothers in the family, all normal, and all relatively short. He is six feet four; no hair on the face; no Adam's apple; and no abdominal hair. Evidently his pituitary and adrenal are compensating for his testicular loss or his small testicle is composed entirely of excellently functionating interstitial cells!

Many of the milder grades of eunuchoid individuals marry, and apparently get along about as well as other sorts of individuals. The lesser grades may produce spermatozoa of sufficient development to impregnate, and consequently have children. There is a tendency in these types to reproduce the eunuchoid type just as there is in the extraordinary early development of puberty a tendency to reproduce that condition.

Treatment of Eunuchoidismus

In the eunuchoid type with normal male sexual libido, the desideratum for treatment is usually increase in the size of the penis. This can be accomplished by special appliances of which my bird cage splint is a good type. These cases often come for treatment for sterility and in the milder grades feedings with anterior lobe pituitary and adrenal cortex may increase spermatogenesis.

In the eunuchoid type with absent or diminished male sexual libido, the treatment should be administration of some of the various testicle or interstitial cell products subcutaneously and if possible and without doubt, best of all is the transplantation of a human testicle.

TABLE OF DIFFERENTIAL DIAGNOSIS OF INFANTILISMS IN THE MALE, EUNUCHISMUS IN ITS DIFFERENT FORMS, AND EUNUCHOIDISMUS

From B. ONUF

Infantilismus. Of the Lorrain Type in the Male.	Eunuchoidismus. Developmental or in other ways congenital.		Acquired.	Eunuchismus.
	Pseudo-Hermaphroditic.	Monosexual.		
Beard and mustache absent or represented by a few hairs only at age of full maturity. Features delicate. Teeth appear late, are often eroded. Expression childlike.	At age of full maturity, or at any age, beard and mustache are entirely absent, or represented by a short lanugo. Face becomes prematurely senile, its skin being yellowish, kid-leather-like in consistency, atrophic, with radiate or vertical wrinkles of upper lip, as in women. Hair of scalp turns prematurely gray. In younger individuals, especially below 25, face may be ruddy, full, but showing sometimes already incipient wrinkling. Expression often effeminate.			
Voice thin and rough.	Thyroid cartilage not prominent. Voice of higher pitch, subdued and gentle, more frequently strident, rasping, sometimes a pleasant tenor.			Voice high-pitched; that of child or boy.
Panniculus adiposus diminished.	Panniculus adiposus varying. Skin may and may not resemble the female in character.			Skin white and soft. Panniculus adiposus usually increased. Tendency to swag belly.
Musculature delicate.	Muscles are usually markedly flabby.			
Stature small, thin and delicate.	Stature sometimes undersized, but tall, slender types prevail.			Stature usually tall. Forms rounded. Limbs long with relative shortness of humerus. Hand slender.
	Hands apt to be of female type in shape.	Hands more frequently of male type of shape.		

The changes characteristic of infantilismus are in Fournier's opinion the result of hereditary syphilis.	Thorax female, tapering downward. Narrow waist. Breathing usually costal.	Thorax may be female, more frequently it is male. Breathing more apt to be abdominal.	Thorax short.
	Pelvis prevalently female; ilia everted; hips broad; thighs convergent.	Pelvis may be female; often it is male.	
Axillary hair absent or sparse and short.	Axillary hair usually less developed than the pubic hair		Axillary hair absent or very sparse.
Pubic hair absent or sparse and short.	Pubic hair sparse and short, sometimes only slightly sub-developed, but female type of distribution, i. e., area of hair cut off in a horizontal line towards abdomen.	Pubic hair is on the whole better developed than in congenital cases, the better so the later in life the testicular atrophy is acquired.	Pubic hair absent or sparse and short.
Breasts aplasic.	Breasts usually approaching female type.	Breasts frequently, but not necessarily approaching female type.	

Compensatory Action

As we have seen from the study of excess of early development of puberty, there is a marked reciprocal action between the pituitary, the adrenal, and the testicle in regard to excess secretion and the early development of puberty.

In castrated individuals a small percentage retain their sexual libido and do not tend to become extremely fat but grow tall. This condition was investigated by Livingston in rabbits, and he found that his rabbits were of two types, those that increase markedly in weight and become very fat, and those that do not. This corresponds with the two types of eunuchs, the fat type and the tall type. His work was very accurate, and in the tall type he showed an absolute increase in weight of the pituitary in proportion to body weight, whereas in the fat individuals there was no such increase in weight. In the adrenal the changes were less marked, and there was more uncertainty as to the effects on the adrenal of castration, although there was a tendency toward hypertrophy.

Data available as to the conditions of the thymus in cases of precocious puberty show that it is usually atrophied. In conditions of delayed sexual development the thymus persists longer than normal. The thymus is supposed to have anti-sexual action and inhibit the development of secondary sex characters.

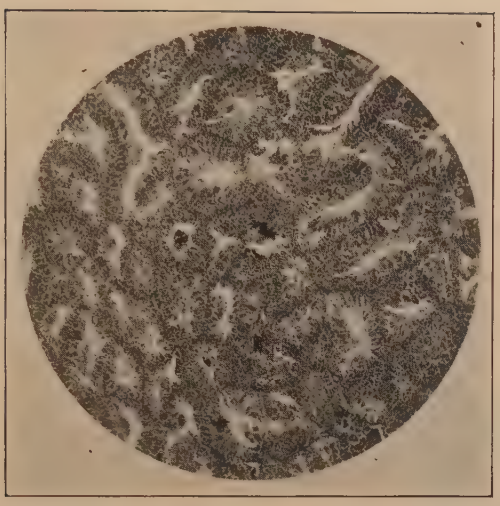


Fig. 29. Photomicrograph of a testicle removed from a cockerel two months old and placed in a two months old pullet on the site of the removed ovary. Nine months thereafter the bird was killed and the grafted testicle removed. It had increased in volume about 7 times and, as can be seen in the photomicrograph, was in active spermatogenesis with excellent preservation of all the testicular elements. The bird showed the spurs, comb development, and plumage changes of the male.

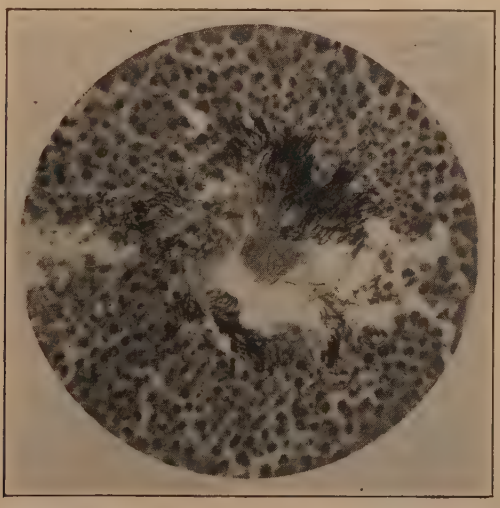


Fig. 30. A high power photomicrograph of above showing the formation of spermatozoa in the transplanted testicle.

Satyriasis

The psychic centers have a marked influence upon the sexual libido. If an individual's thoughts are concentrated upon sexual matters, there is usually a response by an increase in libido. When this condition becomes markedly pathological, it is termed satyriasis, and is due to a stimulation from the higher centers in the brain. Necessarily, the testicular tissues must be normal to enable them to respond to this stimulation by an excess secretion. The fact that fear and worry over the individual's sexual abilities oftentimes produces inability to perform coitus properly is an interesting fact in the light of modern endocrinology, and to my mind at least, suggests, if it does not absolutely prove, that the sexual libido is dependent upon secretion from the interstitial cells. It is well known that fear, anxiety and worry check secretions of other organs and render them temporarily functionless. The stomach is a well marked example of this.

Fig. 31. Barred Rock pullet whose ovary was removed, and in place of which two testicles were transplanted on the ovarian site. Note the enlargement of the head, comb, wattles, ear-lobe, the curved tail feathers, saddle feathers, spurs, and hackle characteristic of the male. This bird was three months old when operated upon and when the photograph was taken was ten months old.

Is it not possible that the real etiology of psychic impotence is a similar phenomenon? Of course, at present we have no definite means of proving this, but with careful clinical examinations and future experimental work this theory may be proved.

Summary

The testicle is an organ having both an external and an internal secretion. The structures producing the external secretion are extremely sensitive to nutritional changes in the testicle, to changes in position of the testicle, and to nerve lesions involving either the centers or the nerves themselves. The structures producing the internal secretion are extraordinarily resistant to all these adverse conditions. They persist and function as small groups of cells in any location of the body wherever they can receive nourishment.

Puberty is determined when the internal secretion of testicle reaches a certain predetermined amount. This can be accelerated as to time by excess function or an increase in number of normally functioning interstitial cells. It is possible to do homo and auto transplantation of the testicle with fair success as regards the preservation of the structures producing the internal secretion. As regards the preservation of the spermatogenic structures, I have been successful in chickens, others have been successful in frogs. In mammals and humans there has been less success. The administration of fresh or dried testicle, adrenal gland and pituitary gland will stimulate both sexual libido and spermatogenesis.

SECTION V

The Prostate Gland as an Endocrine Organ .... *David I. Macht*

Introduction—Anatomical Considerations—Physiological Considerations—Evidences of an Internal Secretion—Effect of Prostate Feeding on the Growth and Development of Tadpoles—Prostate Feeding to Higher Animals—Action of Prostatic Extracts on Isolated Genito-urinary Organs—Thromboplastic Properties of the Prostate Gland—Effect of Prostatectomy on the Behavior of Albino Rats—Effect of Prostatectomy on the Neuromuscular Efficiency of Rats—Summary.

The Prostate Gland as an Endocrin Organ

DAVID I. MACHT

BALTIMORE

Introduction

Even a cursory examination of urological literature will reveal the striking fact that while articles dealing with the prostate gland are innumerable, very few of these, indeed, throw any light on its function. The vast majority of papers to be found in genito-urinary journals deal, for the most part, with the clinical symptomatology and surgery of the prostate gland, and occasionally with its normal and pathological anatomy, but hardly ever will an investigator come across a physiological contribution in connection with this organ. In the present chapter the author purposes to review briefly what little knowledge there is on hand concerning the physiology of the prostate gland on the one hand, and the question of its internal secretion on the other. In this connection, a brief review of the literature on the subject will be first made and this will be followed by an exposition a little more in detail of a number of original investigations which have been conducted by the author in the past few years.

Anatomical Considerations

The prostate gland of an adult man is a compact organ, weighing, on an average, about 30 grams, and having the form of a large horse chestnut. Its anterior portion is pierced by the urethra and the two vasa deferentia traverse part of the gland and open into this pars prostatica of the urethra.

The greater part of the prostate (about 5/6 of the total volume, according to Walker) consists of from 30 to 50 lobules of glandular tissue. The prostatic glands are for the most part tubular, with alveolar appendages, and their ducts, some 15 to 32 in number, open in the *colliculus seminalis.* In between the glandular tissue is found a considerable amount of smooth muscle, as well as lymphatics, blood vessels and nerves. The innervation of the prostate is a double one, the gland receiving fibers from the nervus erigens and nervous hypogastricus. The finer nervous end organs have been studied by Timofeew, who found in the prostate, in addition to the or-

dinary nerve endings, some special bulbous structures of great interest.

As is well known, the secretion of the prostate gland is a thin, cloudy, milky fluid, slightly alkaline in reaction, possessing a characteristic odor. The secretion contains albuminous bodies and occasional so-called amyloid corpuscles, but no mucin.

The size of the prostate gland varies enormously in different species of animals and also at different ages of the same individual animals.

Physiological Considerations

The variations of the development of the prostate gland at different ages of life suggest at once a relationship between its function and the sexual life of the animal. This is further corroborated by the interesting observation that the prostate gland is comparatively very much larger in those animals which are highly reproductive than in others which are much less so. Thus, for instance, the prostate glands of the rat, guinea pig and rabbit are much larger in proportion to the weight of those animals than the prostates of cats, dogs, oxen, horses or men. The author has often extirpated the prostates of rats and found them to weigh as much as 200 mg. or more, or about 1/500 of the total weight of the animal. One need only compare this figure with the average weight of the prostate in man, which is about 1/2,000 of the weight of the body, to appreciate this enormous difference.

The preceding observations have led investigators to suspect that the prostatic secretion bears a direct relation to the life of spermatozoa, and this is the one positive physiological fact in regard to the function of the prostate gland that has been established by the work of Fürbringer, Steinach (*a*), Exner, and, more recently, George Walker.

Evidences of an Internal Secretion.—While the above properties of the external secretion have been regarded as the sole function of the prostate gland, as, for instance, succinctly described by Bogdanow, the increasing importance of the new science of endocrinology directed the attention of various investigators to a possible internal secretion of the organ. The earliest evidence in favor of such a view was advanced by two French observers, Serralach and Pares, in 1907. These authors found that after extirpation of the prostate glands in dogs there was a cessation of the secretion of the preputial glands, a temporary cessation of spermatogenesis and testicular atrophy. These phenomena could be prevented by the injection of glycerin extracts of the prostate. Apparent significance of the work of these observers was somewhat diminished by the criticism of Haberern, who called attention to the fact that it is practically impossible to extirpate completely the prostate gland in dogs.

Experiments with glycerin and aqueous extracts of the prostate gland have been made by Thaon, Posner and others, who found that such extracts are toxic on intravenous injection, producing a powerful rise in blood pressure, which is followed by a secondary fall and a standstill of the heart. More recently, Legueu and Gaillardot made similar experiments with extracts of hypertrophied prostatic glands, and found them to be even more toxic.

Vishnevski reports that prostatic secretions exert an influence on phagocytosis.

Perhaps the most convincing argument or evidence in favor of an internal secretion of the prostate is afforded by the observations of the present author concerning the effect of prostate feeding on tadpoles.

Effect of Prostate Feeding on the Growth and Development of Tadpoles.—Gudernatsch was the first to call attention to the remarkable influence exerted by the feeding of thyroid and thymus glands on frog's larvæ. That observer noted that feeding of thyroid glands produced a dwarfing or shrinkage in size of tadpoles on the one hand, and a very rapid differentiation or metamorphosis of tadpoles into frogs on the other; while feeding of thymus glands retarded metamorphosis and at the same time stimulated growth, with the resultant formation of giant tadpoles. These observations have since been confirmed and extended by Rogoff and many other investigators. Gudernatsch and other observers have also studied the effect of feeding of other organs and glands on the development and growth of tadpoles, and have found that the above interesting effect of thyroid feeding was not produced by any other gland. Recently, however, McCord (*b*) described a similar phenomenon exhibited by tadpoles fed on pineal gland. So far as the present author has been able to ascertain, no experiments concerning the feeding of prostate gland to tadpoles, or concerning the relation of the prostate to the growth of other animals, are on record.

In connection with a physiological and pharmacological study of the prostate gland and of prostatic extracts, the present author conducted a series of experiments in feeding varicus tadpoles with desiccated prostatic substance. Tadpoles of the following amphibia were employed: *Rana sylvatica, Rana palustris, Rana catesbiana, Bufo lentiginosus* and *Amblystoma punctata.* Experiments on them were begun at different ages, some being used immediately after hatching, others when they were from one day to three weeks old. In every experiment, several tadpoles of exactly the same age and the same species were placed in two vessels. The tadpoles in one vessel were fed prostate; those in the other vessel served as controls. In all experiments the two sets of tadpoles were kept under exactly the same conditions. They were placed in vessels of the same size, containing the same amount of water, and were kept in the same room under the same conditions of temperature and sunlight exposure. Both sets of

tadpoles were fed in some cases on weeds and in others on fresh pig's liver, or on both. The only difference in the treatment between the two sets was that the tadpoles in one case were fed on small amounts of desiccated prostate gland mixed with the water, while the control animals were either given no prostate at all or were fed on other desiccated glandular substances studied as controls. Thus, for instance, in some experiments as a control to prostate feeding, tadpoles were fed on desiccated parotid substance, or ovarian substance, or corpus luteum, or other glands.

Fig. 1. *Rana sylvatica.* Effect of prostate feeding from April 20 to May 19. Ram's prostate was used.

For the study of the prostate gland, desiccated and powdered prostates were used from the following animals: the ram (Armour's preparation), the bull, the steer, and, in some cases, the desiccated hypertrophied prostate of man obtained from the operating room.

The effect of prostate feeding manifested itself in changes both in growth and differentiation of the larvæ. As in the case of the thyroid gland, it was found that feeding with prostate tended to hasten the differentiation or metamorphosis of the tadpoles into frogs. This effect was noticeable in some cases even after a few days. While this stimulating effect on metamorphosis was not as rapid as that following the administration of thyroid gland, it was found that feeding with prostate was not as deleterious to the animals, so that prostatic substance could be administered to the larvæ continuously, whereas, as is well known, feeding with thyroid must be carried on at intervals, lest the animals die. Furthermore, unlike the effect of thyroid feeding, prostate feeding did not cause a diminution or shrinkage in size of the tadpoles, but on the contrary often showed a tendency to stimulate their growth to a size above normal. These effects will be seen in the illustrations.

Fig. 2. *Rana palustris.* Large tadpoles were fed with some ram's prostate for two weeks, and some with parotid gland. No difference in size and development.

The effect upon the size and the metamorphosis of the larvæ was noted in all the frog tadpoles mentioned above, and also in the case of the common toad, *Bufo lentiginosus,* and in a few salamander larvæ which were studied. The stimulation of metamorphosis was, of course, more strikingly evident in the case of those frog tadpoles which normally metamorphose in a short period of time, but was also demonstrable in the case of the bullfrog, *Rana catesbiana,* which ordinarily takes two years to change from a tadpole into a frog. The sala-

mander larvæ which also take many months before they begin to show signs of metamorphosis, gave definite evidence of a more rapid differentiation after feeding with prostatic substance as early as after two weeks, as shown by shrinkage and stumping of the gills and development of fore and hind legs.

A sufficient number of experiments with controls on various species of amphibians have been conducted to exclude any accidental effects in connection with the above experiments. It seemed to be definitely established that feeding of prostatic substance exerts an influence upon the growth and differentiation of tadpoles. This, of course, would speak in favor of an internal secretion of the prostate gland. It is interesting to note that the iodin content of the prostate gland, unlike the thyroid, is but small, and indeed is much less than that of many other glands in the body.

Fig. 3. *Rana palustris.* Feeding of ram's prostate. Note the metamorphosis of the prostate-fed tadpole as compared with the control. April 20 to June 11.

It was furthermore interesting to note the difference in the effects of the prostates from the steer and the bull. As will be seen from the illustrations, the prostate of the steer was weaker in its action than that of the bull. This is, of course, as might have been expected, inasmuch as the prostate of the steer undergoes more or less atrophy after castration. In a few experiments made in feeding with the human prostate from a case of mild hypertrophy of that gland, the same effects on growth and differentiation were noted as those seen after feeding the prostate of the ram (Macht (*b*), 1920).

Fig. 4. *Bufo lentiginosus.* Metamorphosis produced by feeding ram's prostate from May 12 to June 6. Both tadpoles were about a week old at the beginning of the experiment.

Prostate Feeding to Higher Animals.—Following the interesting observations of the growth and development of tadpoles described above, the author undertook the study of the effect, if any, of prostate feeding on some higher animals. This investigation is still in progress. The results obtained so far, however, would seem to indicate that feeding of small quantities of desiccated prostate gland tends to increase the weight more rapidly than normally. Thus, for instance, in two litters of rats of approximately the same age and fed on the same diet it was found that the one group of rats which received a small amount of prostate gland substance mixed with its food (1 to 1,000) showed a distinctly greater gain in weight than the other group which received the same ration minus the prostatic substance. Similar observations are in progress on rabbits, kittens and puppies, but the results are still too incomplete for publication.

Action of Prostatic Extracts on Isolated Genito-urinary Organs.—It is well known that pathological conditions of the prostate gland are also accompanied by disturbances in bladder function. While such disturbances are generally attributed to mechanical causes, it is nevertheless not quite settled whether the prostate gland may not exert some influence on mental investigation was undertaken by the author in collaboration with S. Matsumoto (*d*), which is published in full elsewhere (1920).

The authors studied the influence of prostatic extracts on the contractions and tonicity of various surviving excised genito-urinary organs *in vitro*. The following organs were studied: uterus and fallopian tubes, bladder and ureters, vas deferens and seminal vesicle. Aqueous saline extracts of the prostate gland of the ram, dog, bull, steer and man were used. The results are shown succinctly in the accompanying table, in which the Arabic numerals indicate the minimal doses of the glandular extracts required to elicit the contraction of the various organs, while the Roman figures indicate the number of experiments of each kind that were performed.

It will be seen on studying the above table that *all* of the genito-urinary organs are stimulated *in vitro* by the addition of prostatic extracts, provided a sufficiently large dose is used; but that different organs require different doses of the glandular extract. The uterus and tubes were found to respond to the smallest quantities of such extracts; the bladder and ureter came next in the order of their response to such treatment; while the vas deferens and seminal vesicles required the largest doses of the extracts in order to give any evidence of a physiological effect. As a result of these experiments we must conclude that the prostate gland cannot be regarded as having any specific or marked influence on the tonus or contractions of the bladder through an internal secretion.

Thromboplastic Properties of the Prostate Gland.—A number of authors (Thaon, Gotzl, Legueu and Gaillardot) who studied the effects of intravenous injections of prostatic extracts in dogs and other animals noted asphyxia and other pathological symptoms and signs attributable to intravascular coagulation of the blood. These observations raised the question as to whether the prostate gland may not possess some internal secretions exhibiting thromboplastic properties. The present author, in collaboration with Miss Beulah Wells, undertook an experimental study of the effects of various glandular extracts in general and of prostatic extracts in particular on the coagulation time of blood (1920). The method employed was that described by Howell and McLean. Oxalated plasma and serum from the blood of various animals—man, dog, cat, pig and rabbit—were mixed in various proportions and the coagulation time was determined after addition of prostatic extracts on the one hand and of normal physiological saline on the other. It was found that saline extracts of the prostate gland tended to accelerate the coagulation time;

TABLE SHOWING INFLUENCE OF PROSTATIC EXTRACTS ON CONTRACTION AND TOXICITY OF GENITO-URINARY ORGANS *IN VITRO*

	Bladder.					Ureter.	Uterus.					Fallopian Tube.		Vas Def.	Sem. Vesic.
	Rat.	Guinea Pig.	Pig.	Rabbit	Cat.	Pig.	Rat.	Guinea Pig	Pig.	Dog	Cat.	Pig.	Cat.[×]	Rat.	Rat.
Prostate — Ram.	(2.5)-5.0-8.0	(0.5)-2.0	(0.5)-1.2-2.0	0.6-1.2-	0.5-1.0	4.0-8.0-10.0	0.5-1.0	0.25	0.25	0.5-1.0	(0.25)-0.5	(1.0)-3.0-7.0	0.5	(2.0)-5.0-7.0-	5.0-7.0-10.0
	XVII.	III.	V.	IV.	IV.	VI.	XVII.	VII.	XIII.	XI	XIV.	VI.	III.	XXIV.	XV.[××]
" Dog.	5.0	2.0	2.5-	1.0	1.0	5.0-10.0	0.5	0.3		0.6	1.0	3.0	0.4	7.0-9.0-	5.0-90
	XII.	V.	III.	III.	IV.	III.	VII.	III.		III.	III.	III.	III.	VII.	III.
" Human, Normal.	5.0	1.5	2.5	1.0	1.5	5.0-10.0	0.5-1.0	0.25	0.5-1.0	0.7	0.5-1.0	2.5	0.6	7.0-10.0-	7.0-10.0
	XI. *	II.	III.	III.	IV.	III.	VI.	III.	III.	III.	XXIII.	III.	III.	V.	II.
" Human, Hypertrophic	5.0	1.5	2.5	1.0	1.5	5.0-10.0	0.5-1.0	0.25		0.7	0.5-1.0	2.5	0.5	7.0-10.0	7.0-10.0
	XI. *	II.	III.	III.	IV.	III.	VI.	III.		III.		III.	III.	V.	II.
" Bull.	5.0	0.25				7.0-10.0-	1.0	0.2				2.0		8.0-10.0-	10.0-
	IV.	V.				III.	VII.	IV.				IV.		IV.	IV.
" Steer.	5.0	0.25				7.0-10.0	1.0	0.2				2.0		8.0-10.0-	10.0-
	IV.	V.				III.	VII.	IV.				IV.		IV.	IV.

* In exceptional cases (2 out of 11 experiments) (in both normal and hypertrophic) a slight decrease of tonus was seen.

[×] Pregnant uterus of cat.

[××] 15 experiments were made; in one preparation the dose was 1.5 cc.

but so did the extracts of many other glands. It was furthermore found that the fresher the extract used the more marked were its thromboplastic properties. This led to a chemical examination of a considerable quantity of prostatic substance and the results of the chemical work showed that the thromboplastic properties of the prostate were attributable to the presence in it of kephalin. Inasmuch as kephalin is a constituent of a great many glands and tissues, the thromboplastic properties of prostatic extracts cannot therefore be regarded as specific.

Effect of Prostatectomy on the Behavior of Albino Rats.—It is well known that following the most successful operative extirpations of the prostate gland, many patients are rendered temporarily, and sometimes permanently, inefficient, either mentally or physically, or both. Such deplorable sequelæ of prostatectomy are almost universally attributed by urologists to senility, operative shock, renal insufficiency and other causes. Can such an impairment in mental efficiency be attributed to the extirpation of the prostate gland and the consequent deprivation of an internal secretion elaborated by it? This question is still unanswered. In order to clear up this problem, at least partially, the present author, in collaboration with Mr. William Bloom, has undertaken the following experimental investigation (1920):

Albino rats were trained in the circular maze devised by Prof. John Watson, and their neuromuscular, as well as mental, efficiency was noted. Such rats can generally find their way through the intricate labyrinth of the maze to its center, by the shortest route and in the shortest period of time, after being trained from ten to twenty days. In order to study the effect of the prostate gland on behavior, a series of rats were operated on and their prostate glands were completely extirpated. Such a complete prostatectomy can be easily performed on rats after a little practice, inasmuch as the glands are comparatively very large and are easily reached. For control experiments another series of rats of approximately the same age were anesthetized with ether in exactly the same manner; their abdomens were opened, and the prostate glands inspected but *not* excised, and the wounds were closed. The two groups of rats were then allowed to recover completely and after a period of several months all of the rats were trained in the maze. It was found, on checking up all the experiments, that complete prostatectomy produced no change in the mental efficiency ("behavior") of the animals. In another series of rats the animals were first trained and their prostates were excised after learning the problem. It was found in this case also that after the recovery from operation the prostatectomized animals were not less efficient than those in which a simple laparotomy was performed as a control. As a result of this rather painstaking research, the authors are led to conclude that extirpation of the prostate gland exerts no effect on the behavior of young adult rats.

Effect of Prostatectomy on the Neuromuscular Efficiency of Rats.—The author in collaboration with J. L. Ulrich (1921) has undertaken an investigation to determine the effect of prostatectomy on the neuromuscular efficiency of rats. This investigation is still in progress but sufficient data have already been accumulated to warrant certain tentative conclusions. White rats were trained to run over a tightly stretched rope. This is a rather difficult trick to learn but after repeated trials the animals can run over the rope from one end of a room to the other without slipping and at a very rapid gait. This performance requires a very accurate coördination of the limbs and indeed of all the muscles of the body, as can be noted by comparing trained rats with untrained ones. Two series of experiments were made: In one series fully developed adult rats were first trained to run on the rope and after they were perfectly accomplished in this respect their prostate glands were completely extirpated. After recovery from the operation the rats were retrained again and after a few trials ran over the rope equally as well as before the operation. In a second series a number of young rats were first prostatectomized and after recovery from the operation the authors began to train them on the rope. It was found that these rats could not learn the rope problem even after a great many trials, whereas non-prostatectomized normal rats learned the rope problem after a definite period of time. Prostatectomized animals showed a distinct weakness of the muscles, especially those of the hind limbs. This was not due to the operative technique inasmuch as other rats on which laparotomy was performed, when, for instance, the testes were excised, did not show such muscular incoördination and weakness.

The authors then undertook to feed the prostatectomized rats on certain glandular tissues and the results obtained after feeding seemed to show an improvement of their condition. These latter experiments, however, are still in progress and will not be described in detail in this place.

Summary

An examination of all the data concerning the prostate described above reveals on the one hand certain negative results and on the other some data which speak in favor of an internal secretion of that gland. It will be noted that no relationship between a prostatic hormone and the tonicity and contractions of the bladder and other genito-urinary organs could be found. Again, it will be seen that the thromboplastic properties of prostatic extracts are attributable to the presence of cephalin in that gland and are not specific for that organ. Lastly, the experiments on the rats in the circular maze seem to indicate pretty conclusively that the extirpation of the prostate gland bears little or no relation to the behavior of the animals.

On the other hand, the experiments on the tadpoles, revealing a distinct influence of prostate feeding on the growth and development of those animals, and the data so far in hand concerning prostate feeding in higher animals, speak very strongly in favor of an endocrin function of the prostate gland. These experiments, together with those of Serralach and Pares, would seem, in the author's opinion, to be the chief evidence in favor of such a function. Macht and Bloom (1920) have also noted an atrophy of the testes in rats in which the prostate glands were extirpated. Inasmuch as the prostate gland can be completely excised in this animal, the observations of these authors sustain the findings of Serralach and Pares. The experiments with prostatectomized rats on the rope problem (see above) are as yet incomplete, but nevertheless seem to offer additional evidence in favor of the production of an internal secretion by the prostate. There seems, therefore, to be considerable evidence in favor of an endocrin function of the prostate, and the subject warrants further investigation.

SECTION VI

The Female Gonads and Their Diseases

Anatomy, Embryology, Comparative Anatomy, and Histology of the Endocrine Components of the Ovaries

E. V. Cowdry

Anatomy—The Interstitial Cells of the Ovary—Embryology and Development—Comparative Distribution—Structure—The Corpora Lutea of the Ovary—Anatomy—Origin, Development and Retrogression—Source of Corpora Lutea—Mechanism of Formation—Retrogressive Changes—Comparative Anatomy—Conditions in Avians—Conditions in Mammals—Histology—Cytology—Cell Inclusions. [From the Anatomical Laboratory, Peking Union Medical College.]

Anatomy, Embryology, Comparative Anatomy, and Histology of the Endocrin Components of the Ovaries

E. V. COWDRY

NEW YORK

Anatomy

The Interstitial Cells of the Ovary

The Interstitial Cells of the Ovary.—The so-called interstitial cells of the ovary were first discovered by Pflüger in 1863 and have since been the subject of many controversies. Their occurrence in the human ovary has been conclusively demonstrated by Pinto ('05), Seitz ('06), Cesa-Bianchi ('07), and other workers, though Fränkel ('05), Aimé ('07), and Anna Schaeffer ('11) maintain that they are absent. Aimé ('07) failed to confirm Pflüger's description of interstitial cells in the dog's ovary, and it remained for Popoff ('11) to redescribe them in detail. There is also some difference of opinion with regard to their presence in adult cats, because Anna Schaeffer ('11) was unable to confirm the work of Löwenthal ('88), Fränkel ('05), Aimé ('07), and others. Many cases of conflicting opinion might be cited; these are merely examples. All the uncertainty is due to the fact that the distinctive properties of the ovarian interstitial cells, insofar as they possess any, have never been carefully observed and tabulated.

We must admit that it is often difficult to identify them in ordinary preparations, particularly when only a few are to be seen, unless one is quite familiar with the tissue. They usually tend to occur in small clumps, which are scattered throughout the stroma (Fig. 1). They possess large spherical nuclei, often excentrically placed, and a fair amount of light staining cytoplasm, which, in preparations fixed in formalin and stained with hematoxylin and eosin, is generally vacuolated on account

of the solution of its fatty constituents. Athias (*c*) ('19, p. 160) has found that the interstitial cells, in the rat, are very intensely stained with iron hematoxylin after fixation in Zenker's fluid, and it is quite likely that the human ovary may react in the same way. Other distinctive points will be discussed later.

Many continental investigators have followed Bouin's ('00) lead in calling these scattered cells the "interstitial gland" of the ovary. Kingsbury ('14) is opposed to this terminology, on the ground that the cells

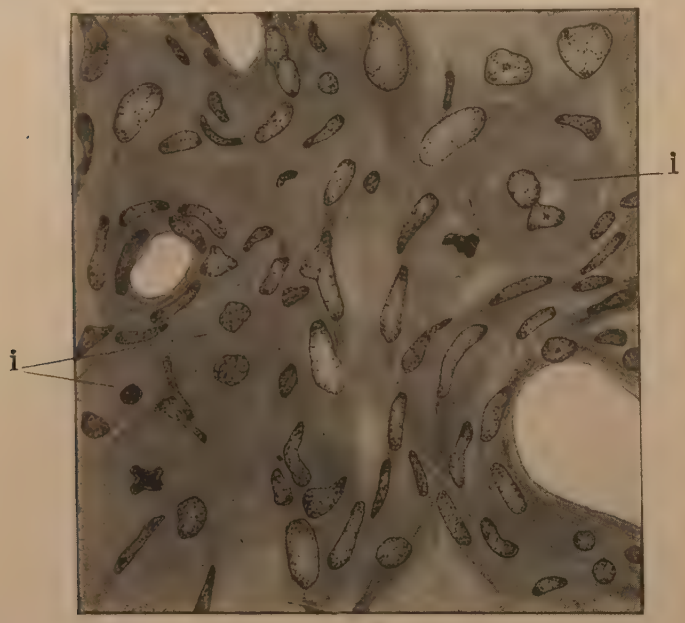


Fig. 1. Interstitial cells (i) in the human ovary (magnification 800).

are not grouped to form a morphologic entity, and because our knowledge of their secretory function is so uncertain. The same objections apply with equal force to the term "diastematic gland," which is frequently used. Van der Stricht's studies on the bat show, however, that the cells do, in some cases, possess true glandular potencies, since they may become grouped together, with the formation of lumina, as shown in Fig. 2, and develop a low grade of polarity.

Embryology and Development

The interstitial cells of the ovary, like those of the testis, are of much earlier development than the lutein cells. In the human embryo they are well formed in four centimeter stages (v. Winiwarter (*a*), '08). They arise as a differentiation of spindle shaped connective tissue ele-

ments. According to Wallart ('07), they reach their highest development before puberty, but persist throughout sexual life, increasing during pregnancy. We know that there is also a considerable development of interstitial cells from the thecæ of atretic follicles, which greatly confuses the picture, because the theca interna also furnishes true lutein cells, so that a distinction between interstitial cells and lutein cells is difficult to make and of uncertain value.

According to Anna Schaeffer ('11), the interstitial cells in the rabbit may be identified by the recations of their fatty droplets as follows:

	Interstitial Cells	*Lutein Cells*
Sudan III	Bright red	Orange
Ponceau	Brownish	Dark red
Indophenol	Bluish red	Deep blue
Nile blue	Stain lightly	Stain intensely

Mulon ('12) has found that the double refraction of the fatty droplets is more marked in the young interstitial cells developing from the thecæ than in the lutein cells and in those of the interstitial gland proper.

Athias (*e*) ('19, p. 151) claims that the fatty inclusions in the interstitial cells are more soluble than those in the corpus luteum.

Owing to the difficulty of devising a satisfactory method for the enumeration of the interstitial cells, the statistical methods, which have been used successfully in the investigation of other endocrin organs, have not yet been applied. Neither has the growth energy of the cells been measured by the inanition method. We are much in need of information along these lines.

Comparative Distribution

The occurrence of ovarian interstitial cells in the vertebrate scale has been by no means satisfactorily determined. It is evident, however, that they are quite as variable as those of the testis. The variations suggest, either that we are wrong in ascribing great functional significance to them, or else that, when they are reduced, the discrepancy is made up by the increased development of some other mechanism. Here, also, quantitative studies are needed. Investigators have not hesitated to group the interstitial cells of the ovary and testis, the lutein cells, and the cortical cells of the suprarenal together, because they all contain closely related, some say identical, lipoids. The logical step is to determine whether there is any compensation, that is to say, whether they vary in unison or independently. It would be interesting also to discover how general is the correspondence between males and females of the same species with respect to the presence or absence of interstitial cells in the gonads. Most of the generalizations which have been advanced thus far are based upon insufficient evidence.

For example, Aimé ('07) attempted to classify the mammals into groups on the basis of the occurrence of interstitial cells in their ovaries. He recognized four. In the first (Solipedes) he believed them to occur only in fetal life; in the second (bats, insectivors and rodents), only in the adult; in the third (cats) in both fetal and adult life; and in the fourth (sheep, pigs, dogs, man, and others) in neither.

Bouin and Ancel ('19) advanced a most plausible hypothesis, to the effect that the interstitial cells are almost, if not completely, absent in mammals which exhibit spontaneous ovulation (man, primates, dogs, etc.), while, on the other hand, they are tremendously developed in mammals of non-spontaneous ovulation (rabbits, guinea pigs, mice, rats, cats). According to this view, the unusual development of the corpus luteum compensates for the absence of the interstitial cells in the first group; in other words, a balance is maintained between the interstitial cells and the periodic corpus luteum, which are, therefore, to be considered as strictly homologous organs, producing the same internal secretion. Unfortunately subsequent researches have failed to confirm the details of Bouin and Ancel's classification of mammals into the two groups, so that we remain absolutely in the dark. An interesting critique is given by Athias (*e*) ('19, p. 185).

Structure

In the human ovary the interstitial cells are arranged without apparent order, except that they show a tendency to be distributed in small clumps, as is illustrated in Fig. 1. They are quite large and are roughly spherical in shape. Sometimes they contain two or more nuclei, but this is the exception, rather than the rule. Indications of the occurrence of amitotic division are not uncommon. Mitoses are, of course, more numerous in young animals. The nuclei are usually large, spherical and generally poor in chromatin, at any rate in the human species. Regaud and Policard ('01) were apparently the first to remark upon the peculiar polychromaticity of the nuclei in their studies on the rabbit and guinea pig. In another study Dubreuil ('06) claims that it is occasioned by the presence of a diffuse, homogeneous substance in the nuclear sap. Athias ('19, p. 165) has found similar appearances in bats, and adds the observation that the darkly staining nuclei are more abundant in old animals. Quite frequently well formed nucleoli may be distinguished. Centrosomes occur in the bat, but I have been able to discover no reference to their existence in man.

The cytoplasm has been carefully studied by many workers. It is crowded with droplets of lipoid, which are dissolved out in routine preparations, giving it a honeycomb appearance. The chemical composition of this lipoid has not been definitely determined. Like the lipoids of the

suprarenal, they appear to differ from other body fats. Parlion, Dumitresco, and Nissipesco ('09) differentiate between them as follows, quoting from Athias:

	Ovarian Lipoid	*Body Fat*
Toluidin blue	Greenish blue	No color
Sections in Flemming's fluid 1-5 minutes	Brownish yellow	Black
Sections in acetone 10 minutes	Soluble	Relatively insoluble
Sections in absolute alcohol warmed 10-15 minutes	Soluble	Relatively insoluble

Mulon ('12) feels that the lipoid is a mixture of phosphatids, fatty acids, and cholesterin. It undoubtedly varies in composition in different animals. It would be well worth while to try to find out whether this

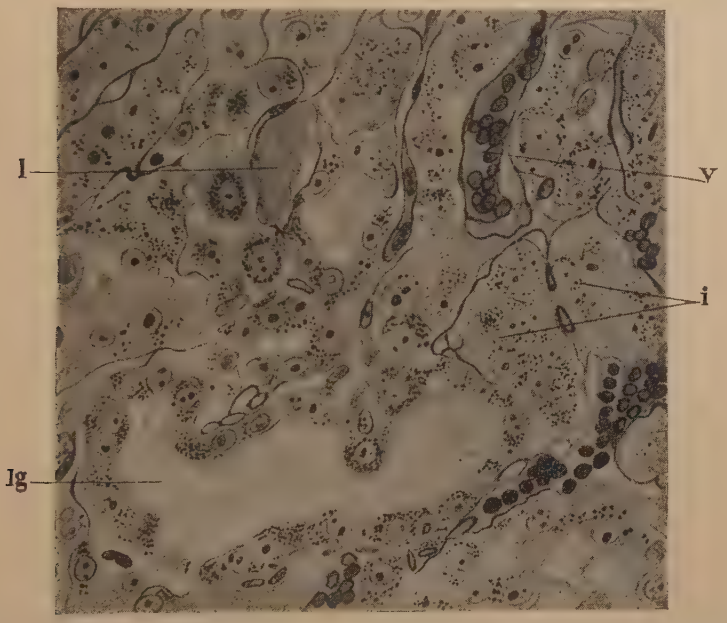


Fig. 2. Section through the covering of a normal bat's ovarian follicle. i, group of interstitial cells; v, vein; and lg, lumen formed through the grouping of the interstitial cells. After O. Van der Stricht.

lipoid differs in any distinctive way, in character or in amount, in animals which Elliot has found to lack doubly refracticle lipoid in their suprarenal glands. Mulon and Mlle. de Jong ('13) have made a special study of the chemistry of the lipoid in the thecal cells of human atretic follicles, and have found that it is doubly refractile, stains with scharlach, is not colored or fixed by osmic acid, and gives the reaction of Salkowsky. In the interstitial cells the lipoid varies considerably in one and the same cell with respect to the size of the droplets, reaction with osmic acid, and solubility. Athias (*e*) ('19, p. 195) shares with others the opinion that it is formed

at the expense of the mitochondria. He claims that, as the interstitial cells develop and become charged with lipoid droplets, there is a proportionate diminution in the number of mitochondria, and that he has been able to follow all the stages in the chemical transformation of the mitochondrial substance into the lipoid droplets. In another place I have pointed out the danger of making such a broad assertion (Cowdry, '18, p. 102).

As far as our observations go, the mitochondria in the interstitial cells exhibit no special peculiarities. They are cytoplasmic constituents of a generalized type.

Hortega ('13) and Cattaneo ('14) have carefully described the reticular apparatus, without bringing to light any special features distinctive of the interstitial cells. Inasmuch as it has been impossible thus far to study this structure in living cells, and since the technic for its demonstration in fixed preparations is notoriously unreliable, it will be advisable to postpone a discussion of its possible relationship to secretory activity until we have more information to go on.

It is interesting to note, in connection with the existence of a problematic homology between the interstitial cells of the ovary and those of the testis, that Aimé has found cells containing xanthin in the ovary of fetal horses bearing a close resemblance to the xanthochrome cells of the testis originally described by Bouin and Ancel. Nevertheless, it is safe to say that, on the whole, pigments are of rare occurrence in the interstitial cells of the ovary.

At present the majority of investigators are inclined to believe that the interstitial cells of the ovary produce a lipoidal secretion in common with those of the testis and the cortical cells of the suprarenal gland, for which the lipoid granules, above mentioned, are usually regarded as the secretion antecedent. As far as we can tell, the discharge of these granules, if it does take place, is not under nervous control.

Mulon has discovered that the cytoplasm often stains diffusely and intensely with iron hematoxylin and other dyes. He observed the same reaction in the interstitial cells of the testis and the cortical cells of the suprarenal, and is inclined to interpret it as indicating the presence of diffuse lipoidal secretion antecedent in solution, which he believes to have been formed from mitochondria. I am unable to agree with him in this explanation, because I have found that the cells of the central nervous system often exhibit a similar appearance, which I have provisionally attributed to a swing of the reaction in them toward the acid side.

Van der Stricht's ('12) investigations of the mode of secretion in the bat are very enlightening. He was able to follow successive stages in the formation of clear droplets within the fatty globules of the interstitial cells, as is illustrated in Fig. 3. These, he claims, pass out of the cells into the intercellular spaces, thence into the lymphatics, and ultimately into the general circulation. His drawings are very suggestive, showing,

as they do, direct continuity between the intercellular spaces, lymphatics, and veins (Figs. 2 and 4); and his further conclusion, that this secretion is equivalent to that formed by the lutein cells, cannot be dismissed lightly, in view of the statement (still unsubstantiated) that heat and menstruation occur in the absence of corpora lutea and that certain changes which usually follow spaying may be inhibited by grafts of tissue devoid of corpora lutea. The only weak point in his work, in my judgment, is the lack of detailed information relating to the microchemistry of the material which he observed in the intercellular spaces, lymphatics, and veins. Kingsbury ('14) gives a caustic criticism of the general conclusion that the secretion is lipoidal. Unfortunately we have as yet no means of

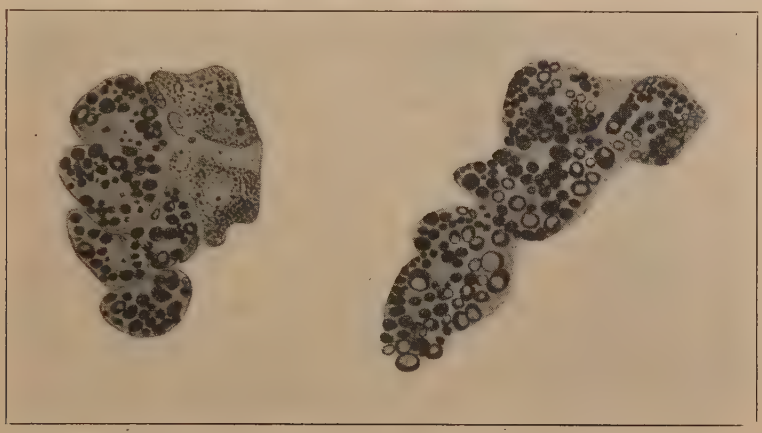


Fig. 3. Interstitial cells of the ovary of a young bat fixed in Benda's fluid and stained with safranin. Note the formation of clear vesicles of secretion antecedent within the darkly stained fat globules. After O. Van der Stricht.

knowing just how far the human condition approximates to that described by Van der Stricht in the bat.

That the interstitial cells of the ovary are physiologically active in some way is attested by the fact that under certain conditions they vary greatly in number. They certainly become reduced during hibernation (Cesa-Bianchi, '07) and increase during pregnancy (Regaud and Dubreuil, '07-'09; Wallart, '07, '08; Cohn, '09, etc.), and Anzilotti ('09) has found that in the rabbit they undergo compensatory hypertrophy in one ovary, following the extirpation of the other. In fact, many animals exhibit compensatory hypertrophy, but in varying degrees, some, curiously enough, being unresponsive and others remarkably sensitive. The interstitial cells tend also to increase in number at puberty. The old idea that it was possible to destroy the reproductive elements of the ovary without injuring the interstitial cells is not substantiated by the recent work of Regaud and Lacassagne ('03).

For the present it is well to hold an open mind regarding the possi-

bility of the interstitial cells forming one or more physiologically active internal secretions. They may still retain, in a more or less reduced degree, some of the properties of the original connective tissue cells,

Fig. 4. Transverse section of zona vasculosa of a bat's ovary. v, vein; l, lymphatic; and lg, lumen formed by clumping of interstitial cells. After O. Van der Stricht.

which, according to Renant, produce internal secretions. These properties may mask and modify their special activity.

The Corpora Lutea of the Ovary

Anatomy

The corpora lutea, at their stage of maximum development, are large rounded masses as much as two centimeters in diameter (Fig. 5). They have a yellowish color, due to a contained pigment, hence the term lutea, from the Latin, luteus, yellowish.

Two chief varieties of corpus luteum are recognized; the corpus luteum spurium, which, in the absence of pregnancy, begins to atrophy about two weeks after ovulation; and the corpus luteum verum (of pregnancy), which remains fully developed for several months.

On section, a striking, perhaps superficial, resemblance to the suprarenal gland is noted, a fact which first led Born to suspect that they possess the power of producing an internal secretion. It may be seen (Fig. 5) that the cells in the outer portion are roughly disposed in columns, simulating those of the suprerenal cortex, between which run the larger blood

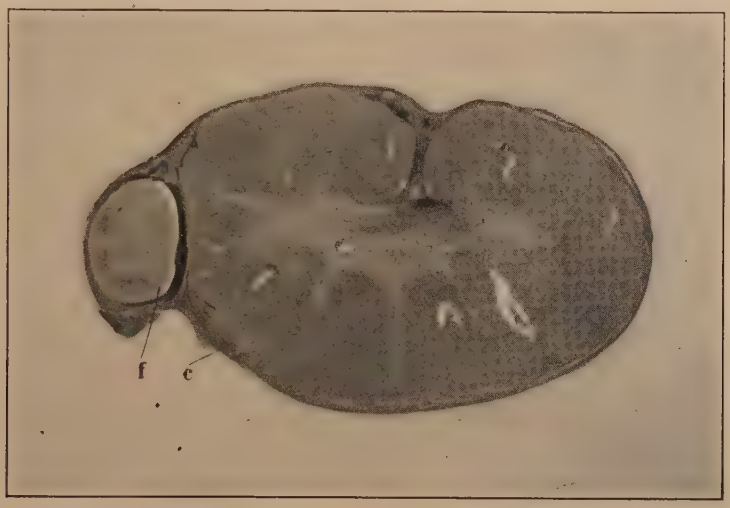


Fig. 5. Section of human corpus luteum (c), with attached Graafian follicle (f) (magnification 5).

vessels, lymphatics, and nerve fibers that have penetrated into the tissue from the ovarian substance. Quite recently a group of French anatomists have revived this idea of similarity by emphasizing the fact that the corpora lutea and the suprarenal cortex are both developed from closely related anlagen, and that they contain apparently identical lipoid material.

Origin, Development and Retrogression

Source of Corpora Lutea.—The corpora lutea are formed from the Graafian follicles after the liberation of their ova, in part at least, by the proliferation of the cells of the zona granulosa and the penetration of connective tissue, blood vessels, nerves, and lymphatics. There is some difference of opinion as to whether the true lutein cells, which form the characteristic yellow pigment, are derived from the granulosa itself, or from the theca interna, or from both. The inadequacy of our knowledge

of the human corpus luteum is lamentable. Corner (*a*) (*c*) describes the conditions in the pig as follows:

Mechanism of Formation.—"In swine the membrana granulosa is retained intact after the rupture of the Graafian follicle. Its cells increase in size without division, their cytoplasm becomes laden with lipoid substances, and they become the larger elements commonly called 'lutein cells' in the fully formed corpus luteum. The membrana granulosa is invaded by blood capillaries from the theca interna, which ramify to form an extensive vascular plexus throughout the new structure. The large lipoid laden cells of the theca interna are increased in number by mitotic division, lose many or all of their fatty inclusions, and pass into the corpus luteum to become lodged between the granulosa cells throughout the whole structure. There is no evidence that cells of the theca interna are ever converted into fibroblasts of the usual spindle cell type, or that they lay down the fibrils of the close meshed reticulum which is present in the corpus luteum. There appears to be good evidence that some of the theca interna cells persist throughout pregnancy as distinct elements of the corpus luteum, but it is not possible to learn by present methods the exact fate of all of them, because of a confusing resemblance between some of the theca and some of the granulosa derivatives."

Retrogressive Changes.—Both types of corpora lutea, the vera and the spuria, undergo similar retrogressive changes. The yellow pigment first disappears, the connective tissue contracts, and the corpora lutea become reduced to the so-called corpora albicantia. These, in turn, decrease in size until only fibrous vestiges, or corpora fibrosa, remain. Atretic corpora lutea are formed through the retrogression of Graafian follicles which have not discharged their ova.

Comparative Anatomy

Conditions in Avians.—The birds deserve special mention, because, as Pearl and Boring have shown, contrary to what one might expect in the absence of pregnancy phenomena, they possess, like mammals, typical corpora lutea. The homology between the two seems to be very close; the avian corpora lutea have the same general plan of architecture, are developed in the same way, and contain the same bright yellow pigment.

In birds it has been shown by Goodale (*d*) that removal of the ovaries causes the development of male plumage; hence the assumption is justified that the ovaries, under normal conditions, produce an internal secretion which inhibits the development of these secondary male characteristics. Boring and Morgan have discovered very striking evidence which confirms this hypothesis in the sebrights, a race of birds in which the males are normally hen-feathered. They have actually found cells in the testes of

the hen-feathered sebrights which are absent in cock-feathered breeds, and which are apparently identical with the lutein cells occurring in the ovary of the female birds. The lack of development of the male plumage in females may, therefore, be attributed to the secretion produced by these cells.

Conditions in Mammals.—In mammals, on the other hand, structural changes in the corpus luteum are definitely associated with the functions of pregnancy and menstruation, which are of course not distinctly represented in birds. It would appear, therefore, that our information is at fault, or else that we have an interesting instance of similar organs exhibiting totally different properties in the phylogenetic series.

Histology

The structure of the cells of the corpus luteum varies considerably in different stages in its development. When it attains its maximum size, and is presumably most active physiologically, they present the appearance in ordinary preparations illustrated in Fig. 6.

Cytology.—We know next to nothing of the finer cytology, much less of secretory changes in the human species, owing to the impossibility of securing properly seriated stages. This difficulty is being overcome in laboratory animals through the introduction of new methods of technic. For instance, Corner and Hurni are applying Evans' method of vital staining, by which all the corpora lutea existing at the time of application are colored, while those arising subsequently remain unstained; and Stockard and Papanicolaou (*c*) are able to predict, through the inspection of the uterus and the vagina of guinea pigs, the existence of all the different phases in the developmental cycle of the corpora lutea in the ovary.

Cell Inclusions.—As might be expected, the cells contain mitochondria, which may easily be stained in the living condition with janus green; they contain as well a definite reticular material, evident only after special methods of fixation and staining, and the characteristic neutral fat, lipoid, and pigment. The best account of the cytology of the corpora lutea is given by Corner (*e*).

Secretory Phenomena.—Working with the bat, Van der Stricht has succeeded in tracing the histological changes involved in the production of two types of secretion, a serous and a lipoid. The serous secretion resembles the liquor folliculi and is formed, after the rupture of the follicle, by the young lutein cells. Van der Stricht observed its elaboration in the form of tiny droplets within the cells, its discharge into the intercellular spaces, and passage into the lymphatics, as indicated in Fig. 4. This secretion increases in amount during the segmentation of the ovum into two or three bastomeres, decreases later, and finally disappears completely

when the egg reaches the uterus. He is of the opinion that it exercises a directive influence upon uterine changes occurring at the same time.

The lipoid secretion is preceded by the accumulation of fat in the lutein cells. At first this fat blackens with osmic acid, but later on, according to Van der Stricht, it becomes changed into droplets of lipoid, which are excreted into the intercellular spaces and lymphatics. These spaces be-

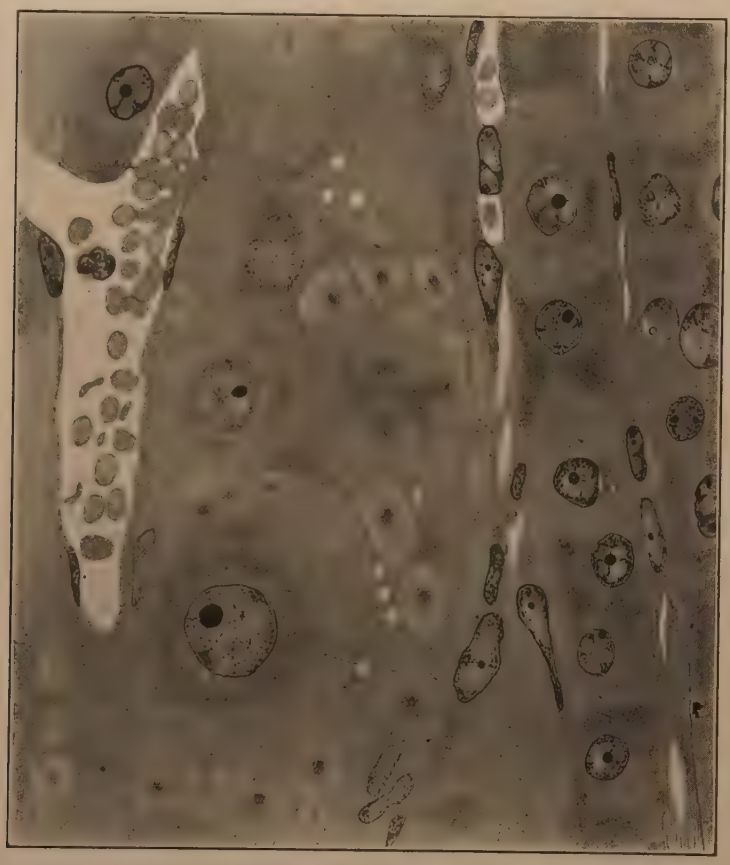


Fig. 6. Cells of human corpus luteum illustrating close relationship to the capillaries (magnification 720).

come so dilated with material that they assume the appearance of veritable ducts, and the living cells simulate true glandular epithelium. That the lutein cells are not definitely polarized, however, is shown by Van der Stricht's observation that the centrosomes are distributed without order in the cytoplasm. Since this lipoid secretion begins shortly after the rupture of the Graafian follicle, and increases gradually until about the end of pregnancy, he concludes that it functions chiefly in bringing about the arrest and fixation of the egg and the development of the placenta. He believes

that it is quite distinct from the hyaline material described by other authors.

It is of course unsafe to say whether these remarkable conditions in the bat have any close counterpart in the human species. Up to the present time no progress has been made in the investigation of structural changes in the corpus luteum induced experimentally. All our information is based upon the doubtful action of extracts and the existence of a more or less close association between seemingly parallel changes on the corpus luteum and other tissues.

Physiology, Physiological Chemistry, and Experimental Pathology of the Female Gonads (Exclusive of the Mammae and Placenta) . . . . . *Swale Vincent*

The Constituents of the Ovary—Brief Account of the Cyclical Changes in the Ovary and in the Uterus—Normal Physiological Functions—Effects of Early and Late Castration in the Female—Castration—Transplantation of Ovaries—Chemistry of the Ovary and Physiological Action Extracts—Structure of the Corpus Luteum—Chemistry of the Corpus Luteum and Physiological Action of Extracts—Extirpation of the Corpus Luteum—Artificial Production of Corpora Lutea—Artificial Production of Deciduomata—Function of the Corpus Luteum—Influence on the Growth of the Mammary Gland—The "Interstitial" Gland of the Ovary—Some General Considerations in Regard to the Relation between the Internal Secretions and the Female Reproductive Functions.

Physiology, Physiological Chemistry, and Experimental Pathology of the Female Gonads (Exclusive of the Mammae and Placenta)

SWALE VINCENT

LONDON

The Constituents of the Ovary—Brief Account of the Cyclical Changes in the Ovary and in the Uterus —Normal Physiological Functions

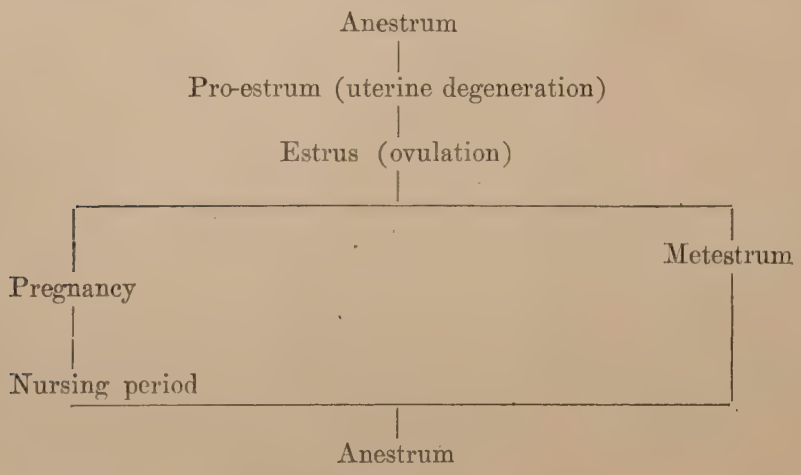
The ovary in mammalia consists of a connective tissue stroma with blood vessels, lymphatics, and nerves, enclosing the Graafian follicles with the ova. At certain periods there are corpora lutea and atretic follicles, and in certain species, the "interstitial gland."

The cyclical changes in the ovary are ripening of the follicle, ovulation, and formation of the corpus luteum. In the uterus we have the well known phenomena of the estrous cycle consisting of growth with glandular activity, regression and interval.

The quiescent period is called the "anestrum." The "pro-estrum" is distinguished by increased vascularization of the reproductive organs, culminating in the estrus (heat), during which only, in the majority of animals, the female will admit the male. In the human subjects and the primates generally, menstruation corresponds to pro-estrum in the lower animals.

If conception takes place, estrus is followed by gestation, gestation is followed by lactation, and this is succeeded in turn by another anestrum. But if conception does not take place, estrus is followed by a metestrum, during which there is a return to the normal on the part of the whole system.

The following scheme is given by Hill and O'Donoghue:—



Effects of Early and Late Castration in the Female
The Secondary Sexual Characters

Castration.—In males it is well known that interference with the discharge of the seminal fluid has no effect on the secondary sexual characters, while removal of the testis has a very marked effect. Similarly, in the female any operation which abolishes the normal passage of the ova down the Fallopian tubes into the uterus has no influence on the secondary characters, while removal of the ovary results in the changes about to be described. These facts are the basis for the theory of internal secretions as applied to the gonads.

Our knowledge of the effects of extirpation of the ovaries before the age of puberty in the human subject is very limited. A large number of operations must have been performed in which female children were deprived of both ovaries, but there seems to be no systematic account of them. Marshall states that double ovariotomy, if carried out before puberty, besides preventing the onset of puberty and the occurrence of menstruation, produces noticeable effects on the general form and appearance, as may be seen in adult women in semibarbarous parts of Asia, where the natives perform this operation upon young girls. Such women are said to be devoid of many of the characteristics of their sex, and in certain cases to present resemblances to men. It is stated that these female castrates grow to be tall, the accessory apparatus of the genitalia remains entirely undeveloped, the secondary sexual characters and the breasts do not develop. This account is quoted not only by Marshall but by other writers, and seems to be derived from the observations of Roberts

in the East Indies, though I can find no reference to his writings. The statements on the subject do not appear to be very exact, and it seems likely that the natives simply effect certain mutilations of the external organs. It would appear incredible that savages could successfully perform the operation of double ovariotomy.

In women castration after puberty is frequently performed by gynecologists. When extirpation of both ovaries is carried out, the most noticeable effect is the cessation of menstruation. There is in most cases atrophy of the uterus and vagiña. The external genitals, especially the clitoris, shrink. The effect on the breasts varies in different cases. Sometimes these atrophy, while in other cases they appear to increase in size. This latter appearance, when it occurs, may be attributed to obesity, which is a usual result of the operation. Sexual desire may not be much affected, at any rate for some time. It may even be increased temporarily. But exact information on this point is difficult to obtain.

After ovariotomy the skin is said to become lighter and the hair more luxuriant. The nipples are reduced in size and the pigmentation of the areolæ become less marked.

The effects on metabolism are not certainly known (v. Noorden). In the human subject acute loss of the ovaries leads to a series of symptoms which are usually attributed to excitation of the autonomic nervous system. There are emotional disturbances, headache, fainting, intestinal disturbances, feelings of heat and cold, etc.

It is stated that in some female animals removal of the ovaries leads to the appearance of male characters. Marshall quotes numerous cases in point. Cases are recorded in which female deer possess horns. In these the ovaries were abnormal or the animals were old. Similar cases are not uncommon among birds, which, on growing senile, have acquired some of the male secondary characters. Thus, a duck assumed the plumage of the drake, and a hen took on the secondary characters of a cock. A hen pheasant had male plumage correlated with an abnormal ovary. Numerous other examples are recorded.[1] Such cases are difficult to explain on any other hypothesis than that the secondary male characters are normally present in a latent form in the female, and that the ovaries exert an inhibitory influence over their development. But castration in the male does not lead to the assumption of female characters.

Some further details of the effects of ovariotomy in rabbits have been furnished by Carmichael and Marshall. The extent of degeneration in the uterus was proportional to the time after the operation. After six months the uterus was in a state of fibrosis and contained no glands. The epithelium was much attenuated, and the muscle fibers were broken up. The Fallopian tubes were atrophied.

[1] Full references to the original authorities are given in Marshall's (*f*) book.

When the ovaries were removed from very young rabbits, the uteri remained infantile. The same was the case with the Fallopian tubes.

Ovarian extirpation in dogs results in a marked augmentation in the vasomotor reaction to a standard dose of nicotin, a phenomenon interpreted as indicating hyperexcitability of the sympathetic nervous system (Hoskins and Wheelon). This corresponds with what occurs after ovariotomy in the human subject (*vide supra*). All the foregoing facts show that the ovary has a pronounced influence in helping to develop and to maintain the secondary sexual characters. Although some observers have urged that the effects of ovariotomy (on the uterus, for example) are due to interference with the blood supply at the operation, or to damage to nerves, the evidence as to influence of some kind of internal secretion is now tolerably conclusive.

Transplantation of Ovaries

In the following account the term "autoplastic" is employed when the ovary is transplanted into some part of the body of the same individual from which it was removed. A "homoplastic" graft is one which is made from one animal to another of the same species, while "heteroplastic" is the term applied to grafting from one individual into another of a different species.

In the human subject transplantation of ovarian tissue has been frequently carried out, but from the reports of cases it is not always possible to learn what degree of success has attended the operation. Homoplastic transplantation was carried out, and apparently with success, by Morris (*a*) in 1906. This writer reports the birth of a child in the case of a woman from whom the ovaries were removed, and in whom ovaries from another woman were grafted four years previously.

Autoplastic transplantation of the ovaries in animals was first successfully carried out by Knauer (*a*) (*b*) (*c*) (1896, 1899, 1900), who described experiments upon rabbits in which the ovaries were removed from the normal position and grafted upon the mesometrium or between the fascia and the muscle of the abdominal wall. Some portion of the grafted ovary always died; the rest produced ova which could be fertilized. The atrophy of the uterus produced by castration was prevented by successful transplantation of an ovary. Knauer obtained similar results with dogs.

Grigorieff in 1897 reported pregnancy in four rabbits from which the ovaries were removed and replaced. He also records two cases in which ovaries were successfully transplanted from one woman to another (homoplastic transplantation). Ribbert (*a*) found that during the first months after transplantation the peripheral part of the ovary remained unaltered, but the central part degenerated into connective tissue. Later, however,

the central portion was again found to contain follicles. Halban and Limon found that transplantation of ovaries produced normal development (young guinea pigs) and prevented uterine atrophy (rabbits).

Magnus in 1907 reported the birth of young on the part of a black rabbit, the ovaries of which had been removed and replaced by those of a white rabbit. The markings of the young indicated a "foster mother" influence (i. e., an influence of the animals into which the ovaries were grafted). Guthrie (*a*) in the same year successfully transplanted ovaries from hen to hen. Such fowls laid eggs which were hatched. The chicks partook of some of the foster-mother's characters.

Carmichael has recorded some success from experiments in which the ovaries of rabbits were transplanted to abnormal positions in the same individual (autoplastic transplantation), but there is no evidence in those cases that the transplanted organs exercised any effect in the direction of preventing the degeneration of the uterus.

Marshall and Jolly (1905, 1907) employed rats to see whether any changes could be found in the uterus after transplantation of the ovaries into new situations. In other cases the ovaries were simply removed (controls). The animals were killed and examined at intervals of from one to fourteen months after operation. In the control animals pronounced fibrosis or other atrophic appearances were always found in the uterus. But in the animals in which ovaries had been successfully transplanted into abnormal positions, the uterus was found unchanged. In homoplastic transplantations also uterine degeneration was prevented by a successful ovarian graft.

The transplanted ovaries were normal, except that the germinal epithelium was absorbed. In some cases some degree of degeneration occurred, and the stroma might be normal, while the follicles had disappeared, or most of the tissue remaining might be luteal. The transplanted ovaries showed the same cyclical changes as the normal ovaries. Thus, in animals killed shortly before the beginning of the breeding season large follicles were found in the grafts, while at a later period corpora lutea were present, showing that ovulation had occurred in the transplanted ovaries. In one case an autoplastic graft was found to be normal after fourteen months, while a normal homoplastic graft was composed entirely of healthy ovarian tissue (with follicles and ova) after six months. In these experiments the ovaries were grafted into the substance of the kidneys.

Autoplastic transplantation was found to be more easily carried out than homoplastic. The most successful homoplastic operations were obtained when two rats from the same litter were employed.[2] A. Louise McIlroy (*d*) found that ovarian grafts prevent atrophy of the uterus for a certain time only, but that ultimately degeneration takes place in the

[2] See also Herlitzka (*a*) (1900), Foà (*a*) (1900), Schultz (1900) and Sauvé (1910).

transplanted tissue, followed by atrophy of the uterus. The rate of degeneration varies with the site of implantation; the more vascular the site, the longer the persistence of the graft. Degeneration takes place first in the cells of the corpus luteum, as evidenced by hyaline changes and leucocyte infiltration. The follicles show cystic degeneration. The interstitial cells persist much longer than the follicles, and they appear to control the nutrition of the uterus, as atrophy takes place when these cells are degenerated, and no atrophy when they are present without any trace of follicles. These experiments were carried out on rabbits and guinea pigs. The longest experiments were not continued more than two hundred days. Marshall and Jolly, as we have seen, found a transplanted ovary normal after fourteen months.

Transplantation experiments have been utilized for the study of the relation between ovary and mammary gland. It has been shown by Steinach that, if ovaries are transplanted into young male guinea pigs, the mammary gland develops and forms acini and may even secrete milk. This author believes that the ovarian interstitial cells are responsible for this effect. Athias has confirmed the results of Steinach, though he is not so definite in his opinion as to which constituent of the ovary is responsible for the changes observed. He believes, however, that it is not the corpus luteum which is so responsible.

An interesting paper by Lipschütz (*b*) (1917) gives an account of Steinach's work and some further experiments of a like character, tending to prove that the internal secretion of the sexual glands acts in a sex specific manner, i. e., the male gonad furthers the development only of male sex characters and inhibits the development of female sex characters, whereas the female gonad furthers the development of female sex characters and inhibits the development of male sex characters. From experiments of Goodale (*e*) and Pézard (*b*) (*c*), Lipschütz concludes that the development in birds of the male plumage and the spurs does not depend on stimulation by the male sexual gland, whereas the female sexual gland transforms a male plumage into a female one and inhibits the growth of the spurs. He considers that the male plumage and the spurs are evolved out of the characters of the hypothetical non-sexual embryonic form, without any influence of the sexual glands. The male plumage and the spurs become male sex characters, not because they result from an action of the male sexual gland on the non-sexual soma, but because the development of these non-sexual characters is influenced in the female by the internal secretion of the female sexual gland. So that Lipschütz groups the sex characters of the vertebrata in the following manner:

1. Sex characters not dependent on the "puberty gland" (Steinach) or evolved characters of the non-sexual embryonic form.

2. Sex characters dependent on the "puberty gland," which evokes

these characters by acting on the non-sexual embryonic form by means of augmentation or inhibition.

A useful summary of recent work on ovarian transplantation is given by Martin (1917). In his conclusions he points out that, from the standpoint of practical medicine, the only form of ovarian transplantation which is of real service is autotransplantation. This is of use in reducing the symptoms of the artificial menopause brought about by complete ovariotomy. But the future of tissue transplantation, in the case of the ovary, as well as of other organs and tissues, rests on a solution of the problem of the homograft. It has recently been urged that after extirpation of the uterus vasomotor disturbances ensue with approximately equal frequency whether the ovaries be retained *in situ*, totally ablated, or transplanted, and that retention of ovarian tissue after hysterectomy is of little or no physiological value and may be productive of serious harm to the patient (Graves (*b*), 1917).

Sand (*b*) (1918) has more recently reported that, as a result of simultaneous transplantation of ovary and testis into a castrated animal, he has succeeded in producing a true experimental hermaphroditism (somatic and psychic).

Chemistry of the Ovary and Physiological Action of Extracts

The ovary does not yield to extracts any substance of such special character and importance, as, e. g., adrenin. Nor does a chemical investigation reveal the presence of any unusual ingredients as, e. g., iodin, in the case of the thyroid.

The physiological action of extracts is the same as that of extracts from tissues generally, viz., a lowering of the blood pressure due to vasodilatation in different regions of the body. The active substance is soluble in alcohol and in ether, as well as in water. According to Champy and Gley, there is a considerable difference in the activities of extracts from different animals. Thus the extracts of the ovaries of the cow, sow, and rabbit are very active, those of the dog and the human subject are only slightly active, while the sheep and the mare yield inactive preparations. The chemical substance to which these effects may possibly be due is B-imidazolylethylamin (histamin, Vincent (*c*), 1918; Dale, 1911).

Hallion injected extracts of dried ovaries in doses of five milligrams into dogs and recorded a fall of the blood pressure, diminution in volume of the kidney and nasal mucous membrane, and a marked increase in the volume of the thyroid gland. It is very doubtful whether this result is specific for ovary.

Ovarian extracts have been stated to be toxic, and there can be no

doubt that, if large doses be administered to small animals, serious results may accrue, as in the case of other tissue extracts. Extracts of ovary hinder the coagulation of the blood both *in vitro* and in the circulating blood.

It is said that ovarian extracts have a well marked effect upon metabolism. Administration of ovary substance produces no effects upon gaseous metabolism in normal sexually mature animals, but in castrated animals, both male and female, the reduced metabolism may be restored to normal, or even rise thirty to fifty per cent above this level (Löwy and Richter (*a*)). According to Beloff, extracts of ovaries freed from corpora lutea give rise to an increase in the oxygen intake and the nitrogen excretion, while preparations from the corpora lutea themselves induce diminution of oxygen intake and increase in the elimination of water. The effects of ovarian material on the carbohydrate and mineral metabolism are not very clearly indicated by the results of experiments so far performed.

It is not safe to allege that any of the above effects are certainly characteristic of and specific for ovarian substance. Many of the same results, at any rate, may be produced by the giving of other organ and tissue extracts. It has been supposed that the ovary has a specific action on uterine muscle, since the contractions of the uterine muscle of the cat exhibit increase in frequency resulting from local action of ovarian extract (Barry, 1915-16).

In some species, at any rate, a part of the effects described above may be due to the "interstitial gland." So far as I am aware, no investigator has studied separately the effects of administration of ovary without any interstitial gland.

Structure of the Corpus Luteum

The classical description both of the development and of the microscopic anatomy of the fully formed corpus luteum is that of Sobotta (*b*) (*f*). In the mouse, the epithelial cells are large and polygonal in shape, measuring 20 μ or more in diameter. They contain a substance known as lutein, a yellowish fatty substance, which is for the most part disposed eccentrically, but it may almost fill the cell. The peripheral cells are most often free from lutein, while those in the center contain the largest amount. Generally speaking, the older a corpus luteum is, the more of the fatty substance does it contain. The nucleus is rounded.

The body consists of columns of luteal cells separated by intervening trabeculæ, the fibrous tissue of which contains numerous blood vessels. These trabeculæ converge inwards from the surrounding ovarian stroma to a central strand or plug of connective tissue, in which there are no luteal cells occupying the axis of the nodule (see Fig. 1). The columns

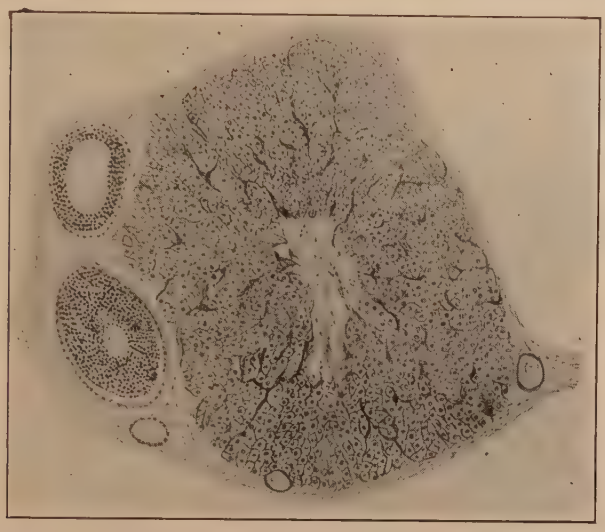


Fig. 1. Section through the ovary of *Dasyurus viverninus*, showing Graafian follicles and corpus luteum. (From Vincent, Internal Secretion and the Ductless Glands, London, 1912.)

of cells bear a very strong resemblance to those of the cortex of the adrenal body. The fully developed corpus luteum is a highly vascular structure. Amongst the cells are numerous cleft-like lymphatic spaces.

The connective tissue is in the form of spindle shaped anastomosing cells. They surround groups of four to five epithelial cells by the anasto-

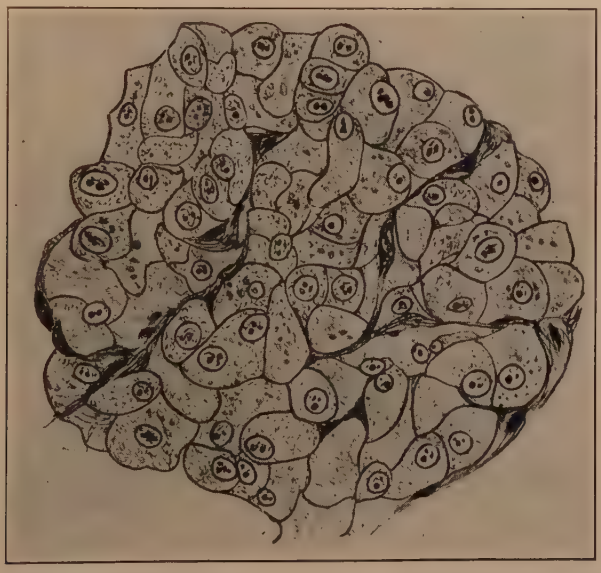


Fig. 2. Portion of corpus luteum of *Dasyurus* under a high power, showing the glandular nature of the constituent cells. (From Vincent, Internal Secretion and the Ductless Glands, London, 1912.)

moses of their processes. Their nuclei closely resemble those of the capillary walls. The connective tissue of the central plug consists of stellate elements. In some animals the fully formed luteal cells are rounded or spindle shaped and may show signs of degeneration.

The luteal cells are, in all probability, derived from the follicular elements. The glandular nature of the organ is admirably shown in the corpus luteum of *Dasyurus* (see Figs. 1 and 2).

Chemistry of the Corpus Luteum and Physiological Action of Extracts

The only substances which are recognized as characteristic of the ovary and corpus luteum belong to the group known as lipochromes. It is not known how far the individual lipochromes are peculiar to the organs in question. Closely allied substances are certainly found in other organs and tissues. The yellow pigments found in animal tissues are related to the similarly colored vegetable pigments. Willstätter and Escher have studied the lutein obtained from egg yolk. The molecular weight was found to be 624, and the formula given is $C_{40}H_{56}O_2$. It is isomeric with xanthophyl, which may be obtained as a by-product in the preparation of pure chlorophyl. It has been stated that lutein is an oxidation product of carotin (obtained from carrots), but this is denied by Serono, who believes that lutein is an oxidation product of the esters of cholesterol with unsaturated acids.

An attempt to isolate the active principles of ovary and corpus luteum has been made by Iscovesco. This writer devised a laborious method of isolation, depending on solubility in different media. One of the substances he claims to have isolated he calls "H.F.b.," as an ether extract of desiccated ovary. It is soluble in acetone. The other substance ("V.D.c.") is alcohol soluble.

Hermann believes that he has succeeded in isolating the active principle of the corpus luteum and of the placenta.

Morley calls attention to the need for more uniform methods in the preparation of extracts. Within the last few years several observers have investigated the influence of extracts of corpus luteum upon the contractions of the uterus and smooth muscular fibers in other places. Stickel reports that parturition in the rabbit is accelerated by injection of extracts of corpus luteum. Guggisberg, on the contrary, obtained inhibition of uterine contractions.

Itagaki states that extracts of corpus luteum generally produce a distinct increase of tone in the surviving uterus of the rat, rabbit, dog, and guinea pig, though occasionally the opposite effect is brought about. The different results are due to the effects of two separate principles, having

antagonistic actions on the uterus. The inhibitory substance is soluble in alcohol, while the augmentory principle is insoluble in alcohol, but soluble in water. Corpus luteum extracts generally produce relaxation of the muscular tissue of the intestine and of the bladder of the rat, but contraction of the whole intestinal tube of the rabbit and the kitten; although, when isolated strips of either the longitudinal or circular intestinal muscle of these animals were taken, they showed relaxation. The evidence given by Itagaki for the existence of two opposing active principles is not very conclusive.

It has been urged that one of the substances manufactured by the corpus luteum is cholesterin. Chauffard (*a*) (*b*) called attention to the presence of this substance in the corpus luteum during pregnancy, and to a cholesterinemia occurring at this time. From these observations he came to the conclusion that the yellow body is a center for the elaboration of cholesterin. But Goñalons (*a*) has shown that the corpus luteum is not the only center for the production of cholesterin.

Extracts of the yellow body have been found to exert a powerfully stimulating effect upon the vas deferens and the seminal vesicles. The vas deferens of the rat is the most sensitive. Contractions occur with extracts as dilute as 1:2500. According to Macht and Matsumoto (*a*) (*b*), the vas does not react to ovarian substance, if no corpus luteum is present. Since the activity of extracts upon the vas runs parallel to that indicated by other clinical and experimental tests, the tissue is recommended for the physiological assaying of corpus luteum preparations. It does not seem reasonable to rely upon what must be an accidental phenomenon as a test for the specific activity of extracts of the corpus luteum.

In 1910 the announcement was made by Ott and Scott that infundibulin from the pituitary body and extracts of thymus gland, pineal gland, and corpus luteum act as galactagogues. So far as infundibulin and corpus luteum extracts are concerned, the results were confirmed by Schafer and MacKenzie. An extension of this work was subsequently published by MacKenzie. Extracts of the corpus luteum of non-lactating sheep were used. The corpora lutea were separated from the rest of the ovarian tissue (which itself was found inactive as a galactagogue) and saline extracts were made from them. The dose generally used was the extract of two corpora lutea in five cubic centimeters of Ringer's solution. The action on mammary secretion, after intravenous injection of the extract, was found to be one of well marked stimulation, but much less in degree than with pituitary extract. MacKenzie states that the galactagogue action, unlike that caused by pituitary, is unaccompanied by any change in the general arterial pressure. One of his tracings, however, shows a preliminary rise of pressure, followed by a distinct fall, as is the case with animal tissue extracts in general. Notwithstanding this, it is

clear from other curves given in the same paper, that a marked action on the secretion of milk may be obtained with doses too small to produce any appreciable effect on the blood pressure. The galactagogue principle is insoluble in alcohol, but is not destroyed by standing in it; its activity is not impaired by repeated boiling nor by standing for some weeks in solution in a sterilized condition. The active substance is present, not only in the corpora lutea of lactating animals, but also in those obtained when lactation is not proceeding. In one case MacKenzie obtained a flow from the gland of a non-lactating cat.

Galactagogue principles can be extracted only from pituitary, corpus luteum, pineal, mammary gland, and the involuting uterus. Other gland extracts appear to be inactive in this respect. MacKenzie reaches the conclusion that the organs above mentioned produce "hormones" possessing the power of stimulating the mammary gland to activity. The evidence in favor of this theory is so far quite inadequate. As the present writer has had frequent occasion to point out, the mere fact that an extract of an animal tissue produces certain pharmacological effects is sufficient perhaps to suggest a possible internal secretion on the part of the tissue, but is by no means proof that such secretion actually occurs.

There are now numerous cases on record in which medical men have treated cases of deficient milk secretion in women by the administration of corpus luteum extracts. The results are said to be good.

Many attempts have been made to replace the internal secretion of the corpus luteum by means of injection of extracts. These attempts have not given very conclusive information, because the extracts have not always been prepared in the same way, and because sufficient control experiments with extracts of other organs have not yet been carried out. Frank found that corpus luteum extract, injected intravenously in sufficient concentration, proves rapidly fatal in consequence of intravascular thrombosis. Corpus luteum substance obtained from a foreign species was without effect on the cyclic changes of the uterus and did not permit the production of deciduomata (vide, p. 566). Loeb (*p*) (1917) states that injection of cow corpus luteum extracts in NaCl solution does not prevent necrosis of the deciduomata, nor does it prolong the life of deciduomata in guinea pigs.

Several years ago the present writer, in conjunction with Dr. F. H. A. Marshall, performed a series of experiments designed to test the theory that the estrous cycle is determined by an internal secretion on the part of the ovary. Extracts were made from ovaries in a proestrous or estrous condition and injected subcutaneously into a bitch at a period as remote as possible from the estrous one. In some of these experiments a swelling of the vulva and other slight signs of the estrous condition were induced, but the results were not decisive enough to war-

rant publication. Since then, however, Marshall and Jolly (*a*) have reported that "heat," or a transient condition resembling it, can be produced by the injection of extracts of estrous ovaries. It is possible that in some of these experiments the extracted ovaries contained corpora lutea and that the effects observed (chiefly consisting of hyperemia of the external genitals) were due to active substances derived from the yellow bodies. Recent experiments by Aschner (*b*), Okintschitz, and others have confirmed the fact that injection of extracts of ovary cause hyperemia and swelling of the reproductive organs. It is not clear from these experiments how far the results are due to corpus luteum and how far to other parts of the ovary. The changes induced do not seem to be true cyclic growth processes, but simply transient circulatory effects. Pearl and Surface have recently shown that the desiccated fat free substance of the corpus luteum of the cow, when injected in suspension in proper dosage into an actively laying fowl, immediately inhibits ovulation. The duration of this effect varies with different birds, from a few days up to two or three weeks. After the bird begins ovulating again the laying goes on unimpaired. The same effect is produced by the injection of extracts of the lutear substance, either intravenously or intra-abdominally. The active substance producing the inhibition is inactivated by boiling.

The whole subject of the physiological effects induced by extracts of ovary, with and without corpora lutea and both with and without interstitial cells, demands renewed careful investigation. In such investigation particular attention should be paid to the mode of preparation of the extracts and the chemical nature of the substances contained in them.

Extirpation of the Corpus Luteum

Prenant (1898) was apparently the first to suggest that the corpus luteum furnishes an internal secretion. He thought that the body influenced general metabolism and prevented ovulation during pregnancy or between the estrous periods. This theory was supported by Regaud and Policard (*b*) (1901), Beard (1897), Sandes (1903), and others, and seems to be firmly established by the more recent investigations of Loeb (*n*) (1911). In sixty-six guinea pigs it was ascertained that spontaneous ovulation rarely occurs within sixteen to eighteen days after a preceding ovulation. In twenty-five animals all the yellow bodies were successfully removed, and in 92 per cent of these all ovulated within twelve to sixteen and one-half days after coitus, showing a marked shortening of the interval between ovulations. Pregnancy *per se* will not inhibit ovulation.

Confirmation of these results is afforded by the experiments of Pearl

and Surface, who injected corpus luteum extract into fowl and prevented ovulation (*vide supra*).

As pointed out by Loeb, the acceleration of ovulation produced through extirpation of the corpora lutea is limited. The next ovulation has to await the maturation of follicles. Without the presence of mature follicles, a new ovulation cannot take place, even in the absence of corpora lutea.

Another discovery has been made as a result of experiments involving extirpation of the corpora lutea. The idea that the corpus luteum might provide an internal secretion subserving the fixation of the ovum in the uterus was first conceived by Gustav Born, and bequeathed to Fränkel to work out. This author (1901-03) came to the conclusion that the corpus luteum ministers in some way to the needs of the gravid uterus. A series of experiments upon rabbits was carried out, the ovaries being removed at intervals varying from one to six days after the occurrence of coition. The rabbits were killed and it was found that the extirpation of the ovaries had prevented the fixation of the embryos or had caused abortion. In other cases the yellow bodies were cauterized out, and similar results were obtained.

Marshall and Jolly extirpated the ovaries from pregnant dogs and rats. In the dogs ovariotomy was performed at intervals of from three days to four weeks after impregnation. The pregnancy was discontinued in every case except one, in which a portion of the right ovary, which contained the degenerate remains of two undoubted corpora lutea, was found post mortem, three days after parturition, when the dog was killed. In this experiment ovariotomy was performed three days after copulation, and parturition occurred fifty days subsequently. Only a single pup was produced, and birth was premature. The pup died after being suckled normally for three days. In rats pregnancy was not continued in any case in which ovariotomy was preformed during the first six days of pregnancy. In other cases, in which the ovaries were removed at periods from the sixth day until near the end of pregnancy, the young were produced normally at full term. Control experiments were also carried out, in which the abdominal cavity was opened up during an early stage of pregnancy and the ovaries cauterized, or in which one ovary was removed and not the other, and in these experiments the course of pregnancy was not interfered with. Marshall and Jolly did not attempt to remove only corpora lutea, while leaving the rest of the ovary. Their experiments fully confirm those of Fränkel.

Marshall points out that there is no evidence that the corpus luteum governs the fixation of the embryo otherwise than by stimulating the uterine mucous membrane to hypertrophy. The general conclusions of Fränkel (*b*) and of Marshall and Jolly have since been confirmed by several authors.

Artificial Production of Corpora Lutea

In rabbits ovulation and formation of corpora lutea do not occur spontaneously, but need the additional stimulus of copulation. Ancel and Bouin (*g*) (1909) discovered that, if the rupture of the follicles be brought about artificially, either by copulation with a male whose vasa deferentia had been ligated, or by mechanical means, it was followed by the formation of corpora lutea and also by a growth of the mammary glands.

The experiments of O'Donoghue (*c*) confirm in the main those of the French writers. Rabbits were taken on the third and fourth days of "heat" and the ripe follicles in their ovaries were burst mechanically. They were allowed to heal up and the animals were killed and examined at varying periods after the operation. But O'Donoghue found that the rupture of the follicles was not invariably followed by the formation of corpora lutea, and when corpora lutea were not produced, there was no growth of the mammary glands (*vide infra*).

Artificial Production of Deciduomata

As we have seen, Fränkel (*b*) and others showed that the corpus luteum produces some change in the uterine mucosa which helps in the fixation of the fetus during the earlier period of pregnancy. It remained for Loeb (1917) to reveal precisely what these changes really consist in. It occurred to this observer that the influence of the yellow body could be cleared up only by performing a series of experiments, in which the changes in the uterus could be studied directly, without the interference of a fertilized ovum. Pregnancy was, therefore, excluded by tying the Fallopian tubes soon after copulation, or by using guinea pigs in which heat had been observed. In the normal guinea pig a spontaneous ovulation takes place at the time of heat in almost all cases. Loeb succeeded, furthermore, in substituting ordinary foreign bodies and other mechanical stimuli for the action of the ovum. It was found that, if such mechanical stimuli are applied to a uterine mucosa which has been previously sensitized by the internal secretion of the corpus luteum, a maternal placenta is produced at the place of stimulation. The mechanical stimulus replaces the ovum in these experiments.

Loeb observed that, even without the presence of a definite and well defined mechanical stimulus, the mucous membrane of the uterus shows some slight overgrowth, due to the secretion of the yellow body. He assumes that the stimuli occurring in normal life produce these changes in a sensitized uterus. In *Dasyurus viverrinus,* a marsupial studied by

Hill and O'Donoghue, in which the corpus luteum is well developed and persistent in the non-pregnant animal, the enlargement of the uterine mucosa is specially marked. It may be, as suggested to me by Professor O'Donoghue, that the effect of a mechanical stimulus is largely to localize the overgrowth and thus help in the development of definite deciduomata.

There is a definite parallelism between the development of the corpus luteum and the cyclic changes in the uterine mucosa. By experimental means a much larger quantity of maternal placenta may be produced than under normal conditions of life.

The results of Loeb have been confirmed by Ancel and Bouin, Biedl, and R. T. Frank.

The secretion of corpus luteum, then, sensitizes the uterine mucosa and makes it capable of reacting to mechanical stimulation. There is a relation between the quantity of the secretion on the part of the yellow body and the degree of response which can be obtained by a mechanical stimulation. The response is only obtained when sufficient secretion to sensitize the mucosa has been poured out. If the stimulus be applied when the body is just beginning to secrete, little effect may be produced. But if the application be made later, when the uterine wall has become completely sensitized, the secretion of the substance goes on for a few more days and increases the reaction. The ovum becomes attached at about the time when the greatest sensitization of the mucosa has been obtained (Loeb).

Several other interesting facts were brought to light by Loeb's investigations. The substance secreted by the corpus luteum and which sensitizes the uterine mucosa is not specific, that is to say, the substance of one individual will cause growth in the sensitized uterus of a second individual of the same species. The effect, however, is less pronounced than in the organism to which it belonged. This difference is supposed to be due to the presence of "homoiotoxins" in the second individual. The sensitizing substance produced by the corpus luteum gives rise to special and characteristic reactions in the different species. The experimental deciduomata in any species have the structure of the maternal placenta in pregnancy. In some animals (rabbit, guinea pig) the effects are confined to the uterus, while in the human subject deciduomata can be produced in the Fallopian tubes in cases of tubal pregnancy. Loeb suggests that the readiness with which extra-uterine pregnancy develops in different species depends, in part at least, upon the readiness with which the stroma of the host responds with the production of a decidua favorable for the development of the embryo.

Deciduomata become necrotic within twenty days, and the cyclic proliferation of the mucosa lasts only a few days. Extirpation of the corpora lutea prevents the deciduomata from reaching full size and

causes earlier and more extensive degeneration of those which develop. The necrosis is largely due to hemorrhage. But deciduomata produced by mechanical means in one horn of a uterus while the other horn is pregnant may persist throughout pregnancy. This appears to be due to a distant effect either of the embryo or the yellow body. If it is due to the latter, then it is clear that it cannot be due to the continuation of the same secretory activity which calls forth the deciduomata, for at the time when the life of the deciduoma is thus being prolonged, the sensitizing substance is no longer produced in the corpus luteum. Either, therefore, there are two quite different actions of the yellow body secretion, one sensitizing the uterus, the other prolonging the life of the deciduoma, or there is only one substance, but this is poured out in different quantities at different periods. The small quantity at the later period is sufficient to preserve deciduomata, but would be insufficient for the new formation of these growths.

Function of the Corpus Luteum—Influence on the Growth of the Mammary Gland

We have seen that the corpus luteum inhibits ovulation, and that it has a sensitizing action on the uterus. Incisions into the uterus made from two to nine days after coitus or after rut, that is to say, at a period when the yellow body has been active for some time, are followed by the appearance of multiple tumors along the line of incision. These have the same microscopical structure as the maternal placenta. The mechanical stimuli, therefore, assume in this respect the function which the ovum exerts under normal conditions. But the corpus luteum appears to have also another important function related to the mammary gland.

Hildebrandt suggested that during pregnancy an impulse is exerted by the developing ovum on the mammary glands, which acts as a stimulus to growth and at the same time protects the cells of the gland from those autolytic disintegrative processes which occur to a large extent in the secretory gland. The matter was put to the test by Lane-Claypon and Starling. These observers made extracts of fetuses by rubbing up with sand, extracting with normal saline solution, centrifuging, and passing through a Berkefeld filter. The animals used for experiment were then injected subcutaneously with the extracts. In virgin rabbits a growth of mammary gland was produced, and in multiparous animals a secretion of milk. The authors believe that their experiments show that the growth of the mammary glands during pregnancy is due to the action of a specific chemical stimulus ("hormone") produced in the fertilized ovum. The amount of this substance increases with the growth of the fetus and is largest during the latter half of pregnancy. Foà (*b*) in

1908 observed that injection of extract of fetal calf caused some mammary growth in rabbits. It is therefore concluded that the effects described by Lane-Claypon and Starling are not specific for a single kind of animal. Heape points out that it is well known that virgin animals sometimes produce milk. Hence, it seems clear that the beginning of the development of the gland dates from some point of time prior to or during pro-estrum or estrus, and occurs normally quite apart from pregnancy, and that since the full functional development of the gland may be experienced by virgin animals, this must occur without any stimulus from a fetus. Heape believes that the source of the stimulus which excites the development of the mammary gland is to be found in what he calls "gonadin," secreted by the ovary at that time, if not in the "generative ferment" which, he holds, governs the activity of the generative glands. The theory of Lane-Claypon and Starling was also criticized by Frank and Unger, who definitely suggested that it is the persistent corpus luteum of pregnancy which produces mammary growth.

O'Donoghue points out that in *Dasyurus* the life of the corpus luteum in the pregnant and non-pregnant animals can be divided into three stages: (1) period of formation, (2) period of growth, (3) period of constancy. The formative growth of the mammary gland also falls into three divisions: (1) commencement of growth, (2) period of active growth, (3) period of constancy. These three periods in the corpus luteum precede by a short time the corresponding periods in the mammary glands in such a manner as to suggest cause and effect. Lane-Claypon and Starling found that removal of the ovaries (containing corpora lutea) is followed by cessation of growth and regression of the mammary gland. As we have seen above (p. 565), O'Donoghue observed that, if follicular rupture is not followed by formation of corpora lutea, there is no growth of the mammary glands. The conclusion seems unavoidable that the hormone causing the growth of the mammary glands during pregnancy and at other times is produced in the corpora lutea.

The "Interstitial Gland" of the Ovary

The "interstitial cells" or the "interstitial gland" have occupied a prominent place in all discussions of ovarian function during the last fifteen or twenty years. It is especially in regard to proved or suspected internal secretion on the part of the female gonad that these structures have received so much attention. The true significance of the cells in question is not known, and much of the confusion at present existing in the literature arises from the fact that the majority of workers on the subject have restricted their inquiries to a narrow field of investigation, while more general considerations have escaped their notice.

Many authors consider the interstitial cells of the ovary and those of the testis as belonging to the same category. But the evidence in favor of this view is very unsatisfactory. The cells of the ovary are, at any rate, much more conspicuous than those of the testis, and the histological differences between the two are sufficient to warrant considerable hesitation in forcing an analogy.

At the outset we are met with the perplexing fact that the interstitial cells are not present in all species. Out of more than one hundred species so far examined, fifty per cent are said to possess none. It is true that some writers are inclined to believe that some trace of the interstitial tissue is always present, though the cells may be very inconspicuous and may be overlooked, owing to the fact that under certain conditions they do not react to ordinary staining reagents. Again, it has been supposed that the cells undergo periodic changes of such a character that at certain times they may vary, being at one time more, and at other times less abundant or conspicuous. The subject of the occurrence or non-occurrence of the interstitial cells in the various species of mammals still requires careful investigation.

The morphological aspects of the question are dealt with in another part of the present work, but it will be useful to mention some papers of recent date from which most of the literature can be collected. In 1916 O'Donoghue gave a good account of the interstitial cells in marsupials. Rasmussen (*b*) (1918) describes the cyclical changes in these cells in *Marmola monax* and gives a full account of the literature. Athias (*e*) in 1919 has published a careful study of the interstitial cells in the cheiroptera.

There seems to be no doubt that the interstitial cells undergo cyclical changes of such a nature that they reach their greatest development during pregnancy and lactation.

As to the origin of the cells in question, there has been much controversy. The history of this will be found in the papers referred to above. Two sources have been urged specially: (1) from the stroma (connective tissue) either directly or indirectly through the theca interna of atretic follicles, (2) from epithelial tissue (germinal epithelium). The majority of writers have favored the former view, but the evidence is by no means convincing, and histologists will be reluctant to admit the connective tissue origin of cells possessing so glandular an appearance. Moreover, even if it be certain that the interstitial cells are directly derived from some of the "stroma" cells, it is by no means clear that these particular elements are themselves of connective tissue origin. Some epithelial structures may easily have become involved in the stroma at an earlier stage. The origin of the stroma cannot be alleged to have been settled in all its details. In any case the interstitial cells are now generally regarded as a tissue *sui generis*.

The fully developed interstitial tissue presents all the appearances of

a typical glandular formation. Its blood supply is abundant, and the cells are polygonal in shape and contain granules. These are of various kinds, as indicated by their staining reaction (O'Donoghue, Rasmussen). There is an abundant chondrioma and enclosures of a lipoid character, siderophil protoplasm, and distinctly polychromatic, large, round nuclei. The chondrioma is made up of chondrioconta and mitochondria. It undergoes important modifications in the course of the evolution of the cell. The granulations, at first few, increase in the later stages; the fatty products are the result of a chemical change in the mitochondrial substance. The lipoid enclosures probably represent the products of secretion (Athias).

The function of the interstitial cells is completely unknown. No discussion of this subject can be useful which ignores the fact that the tissue appears to be absent in large numbers of animals. It may be that a thorough investigation of the occurrence or non-occurrence of the tissue in question in a very large number of species might throw considerable light on the question, especially if due account were taken of any peculiarities in the cyclic function of the reproductive organs in the different types. It is not easy to suggest any direct experimental work which might be expected to elucidate the problem.

In Marshall's (*f*) book on the physiology of reproduction very little is said about the interstitial cells. The author calls attention to the fact that Miss Lane-Claypon has shown that the cells increase in size during gestation. She suggests that the interstitial cells produce a secretion of the same kind as that manufactured by the corpus luteum.

Of late years a great deal has been written about the internal secretion of the interstitial cells, but no hypothesis has been put forward which has much evidence in its favor. No mass of cells which is not muscular or nervous or obviously supporting cells and which is not in connection with a duct can at the present time escape the charge of furnishing an internal secretion.

In 1905 Marshall and Jolly (*a*) concluded that heat in animals is not caused by a secretion of the corpus luteum, but probably by means of an influence exercised by the interstitial cells. This suggestion was repeated in 1911. The experiments of Lacassagne do not support this hypothesis. Heat occurs in animals, even when all the secreting elements of the ovary have been destroyed.

The view which is now held by the majority of writers is that the interstitial cells preside over the nutrition of the reproductive organs and are responsible for the appearance of the secondary sexual characters. We have seen above (p. 552) that extirpation of the ovary interferes with the development of these characters and gives rise to atrophy of the uterus. Successful transplantation may have the effect of maintaining the normal condition. As we have seen (p. 556), Steinach finds that, if ovaries are

transplanted into young male guinea pigs, the mammary gland develops and may secrete milk. He believes that the interstitial cells are responsible for this effect. We have also seen (p. 555) that Louise McIlroy (*d*), after ovarian transplantation, found that the interstitial cells persist much longer than the follicles, and they appear to control the nutrition of the uterus, since atrophy of this organ occurs when these cells are degenerated and no atrophy when they are present.

Among recent writers the above view has been most ably presented by Athias. He recognizes fully the difficulty presented by the alleged absence of the interstitial cells in many species of mammals, but he appears to think that, if a sufficiently diligent search be made, some traces of them may always be found. The majority of workers on this subject are not hopeful that this will be found to be the true solution. We must rather assume provisionally that there are some peculiarities (presumably connected with the sexual cycle) in those species which possess the interstitial cells which demand their activity especially during pregnancy and lactation.

Some General Considerations in Regard to the Relation between the Internal Secretions and the Female Reproductive Functions

Some authors have insisted that the ovaries are not the only organs which determine the secondary sex characters. Thus, Blair Bell (*b*) lays great stress on the fact that "femininity" is dependent on all the internal secretions. The relation of the thyroid to the female genital system is dealt with in another chapter of the present work. The influence of the adrenal cortex is treated by the present writer in a paper which appeared in 1917. There is apparently no direct relationship between the parathyroids and the female sex organs (Pool). The pineal is alleged to have an influence on sexual precocity (Kidd). The pituitary has an influence on many of the metabolic functions necessary for the establishment of puberty (Blair Bell). Paton (*a*) found that thymectomy, performed before puberty, causes a rapid development of the genital gland. The whole subject is complicated by the influence of the various internally secreting organs upon each other. The psychological peculiarities of women are of course partly accidental and dependent on social conditions, but of those which are more fundamental, some depend on the influence of the ovary and others on general metabolic processes, which are largely conditioned by the general reactions of the internally secreting glands.

Robinson believes that it is a secretion produced by the ovarian follicles which is responsible for the estrus. The view has not received general acceptance.

The Rhythm of Gonadal Function with Special Reference to the Relations between Uterus and Ovary . . . . . .

. . . . . *Herbert M. Evans*

The Gonadal Function before Puberty—The Prepubertal Ovary and Its Rôle in the Determination of the Secondary Sex Characters—Rhythmic Gonadal Function in the Adult Female—Introductory—Ovulation—Conditions—Conditions in Man—True Disturbances of Gonadal Rhythm which Are Associated with Menstrual Aberrations—Disturbances Producing Amenorrhea—Secondary Ovarian Impairment—Disturbances Producing Uterine Hemorrhages.

The Rhythm of Gonadal Function with Special Reference to the Relations Between Uterus and Ovary

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I. The Gonadal Function before Puberty

The Prepubertal Ovary and Its Rôle in the Determination of the Secondary Sex Characters.—It is of great interest to know that before the assumption of sexual activity (i. e., the time of puberty) the female gonad, like the male, has not only attained a considerable development and differentiation but has exerted a specific endocrin function, the function of determining the secondary sex characters. The adult ovary besides furnishing ova has also specific endocrin functions, but these are of a more particular nature and concern chiefly changes in behavior (œstrus) and in the structure of the generative apparatus which will insure the fertilization and nourishment of the ovum so that a new organism is assured. We are able to assign some of these functions of the adult ovary to particular tissue components as will be seen from the following account. It is consequently of interest to inquire as to what anatomical elements in the prepubertal gonad are responsible for its endocrin activity in determining the so-called secondary characters of sex. For a long while the structure of the fetal and prepubertal ovary has been interpreted as meaning merely that the gland makes ineffectual efforts to attain its adult rôle, or, in other words, that abortive attempts at ovulation are continually going on. Newer studies would tend to show that such a method of expression is unfortunate; that before puberty is reached not only are none of the phenomena more immediately connected with ovulation ever observed but that the processes which do take place need not be considered as aborted ovulation. It is a fact that in the prepubertal ovary primordial and other follicles in various degrees of development or degeneration are present in abundance, but that under no circumstances does follicular rupture occur nor are there found those peculiar structures consequent upon ovulation, the corpora lutea. The follicles in the prepubertal ovary may attain a consid-

erable size but they invariably degenerate by death of both the ova and granulosa, whereupon the next adjacent enveloping cells of the ovarian stroma—the cells of the so-called theca interna—undergo a peculiar hypertrophy and activity, surviving for a very considerable time after the follicle about which they were first formed has entirely disappeared. So extensive are these peculiar processes which attend prepubertal follicular degeneration or atresia, that the gland comes to possess throughout its substance many cell clumps and strands formed by these cells of the theca interna. Indeed, even in the postpubertal life of many mammals, these cells may be similarly so abundant and so diffuse as to constitute at times the main mass of tissue of the ovary. These are the ovarian *interstitial cells.* Their origin from the theca interna was first clearly made out by the French histologist Limon (*a*). It has been claimed that they alone are responsible for the gradual unfolding of the secondary sex characters during early development, a thesis which has been especially defended in great detail by Lipschütz. Their function would be then presumably enormously increased during that time of "flowering out" of the sex characters known as the puberty period itself. Quantitative studies which would show a great increase of such cells at exactly this time are unfortunately not at hand, and there is even evidence, indeed, that with the occurrence of the first ovulation, function of the interstitial substance rapidly recedes in importance. Furthermore, we do not possess proof that the secondary sex characters are all delayed in expression until the formation of the interstitial cells by follicular atresia can be demonstrated as occurring or as having taken place.

But an identification of the ovarian interstitial cells with the development of characters distinguishing the female sex has been supported by other studies than those on embryology and growth. Steinach and Moore have transplanted ovaries into young castrated males and believe that one may thereby effect changes in the sex characters of the host involving the surrender of masculine and the acquirement of feminine traits which further express themselves, for instance, in the modification of such a general phenomenon as the rate of growth. The ovary normally retards the growth of the female and exercises the same effect when transplanted to castrated males. Steinach and Athias indeed have demonstrated that in such experiments there may ultimately appear a hypertrophy of the mammary glands of the male host and a true secretion of milk so that he is able to adopt offspring. The ovaries in such transplants do not for a long time depart greatly from the normal, as found by Sand and by Marshall and Jolly, and as I have been able to confirm in experiments with Long; for a time they continue to ovulate and form corpora lutea regularly but Steinach and Lipschütz describe them as having eventually lost all trace of true luteal structures and as coming to possess merely a great number of obliterated follicles which are peculiar hybrid growths in

which the overwhelming proportion of the tissue consists of inner thecal or interstitial cells. These authors admit, however, that certain of the follicular granulosa cells survive and enlarge. Sand, who has found more normal structures in the ovarian transplant, nevertheless describes an increase of atretic processes, so that internal thecal or interstitial cells come to be much more abundant.

The interpretation put upon such experiments has been that in these cases the specific egg-producing activity of the gonad is no longer utilized but has been supplanted by a reversion to the prepubertal form—the form in which the interstitial cells are predominant—and that the expression of feminine secondary sex characters in the male host is due primarily to these cells. Further, Steinach and Holzknecht [1] claim that not only the transplanted ovary but one submitted to the action of x-rays also shows a degeneration of eggs and follicular apparatus and a survival and accentuation of the thecal or interstitial cells.[2] When a correct ovarian Röntgen dosage was administered to young females and a considerable time interval allowed to transpire, there resulted a singular and marked mammary enlargement which finally expressed itself in true milk secretion. The ovaries of such animals are said to contain few or no normal follicles or corpora lutea but are full of the same strange hybrid of proliferated thecal and granulosa cells. Here again the pronounced effect of the ovary upon the mammary gland has been referred exclusively to the activities of the so-called interstitial cells.

It were well to call attention to the fact that in all of the cases which have been cited, i. e., both in normal development and in the experiments which have been detailed, the *interstitial* cells are not and cannot be clearly separated from the other fundamental ovarian tissue of equal importance—the follicular tissue of eggs and granulosa cells. We know that follicular tissue in the adult in its cyclic growth produces very pronounced effects (see below) and it would consequently appear unwise to deny it any participation in the function of the ovary before the time of puberty.[3]

Be that as it may, and while one may be in doubt as to the exact proportionate rôle of the follicular and interstitial tissue, we know that the youthful ovary is responsible for all that important series of physiological effects designated as the development of secondary sex characters. The newer experimental work on the ablation of the sex gland in early

[1] So also Hüssy and Wallert, Hewer, and Aschner.

[2] This had been previously demonstrated by Bouin, Ancel and Villemin.

[3] Where interstitial cells are found, follicular tissue has always existed previously. One may also inquire as to the rôle of the egg cells themselves, which Meyer and Schroeder believe to be the real source of control of the cycle in the adult. Meyer has accordingly revised the original sentence of Helmont "Propter solum uterum mulier est quod est" which Virchow had improved by substituting the ovary for the uterus ("Das Weib ist eben Weib durch seine Generations-drüse") by now substituting egg for ovary—"Propter ovulum mulier est quae est."

stages has firmly established this general conclusion. Furthermore, the varying effects of castration have become intelligible to us on the assumption of the existence of an asexual embryonal form (Tandler, Gross, Keller). This latter hypothesis, while possessing opponents, seems best fitted to coördinate all of the facts. According to it the germ cells of the new individual, the sex of which has been determined by chromosome constitution, begin to affect the somatic cells at a very early and certainly embryonic period,[4] though the soma possesses certain inherent tendencies to express itself in a neutral, or asexual, form. Could castration be carried out sufficiently early, such a neutral form would always result, a single sex-undifferentiated form which would be characteristic of the species. Either the male or female may exhibit traces of this embryonal form, and the testis or ovary may either act to suppress the neutral embryonal form or to create a new form peculiar to the particular sex. Only actual experiment will discover whether in any given species a supposed sex character is actually such or is the survival of the common or neutral form. A survey of such a viewpoint is furnished by the appended table.

GENETIC SYSTEM OF THE SEX CHARACTERS

(According to Lipschütz)

	Instances	
	Mammals	Birds
1. So-called sex characters not dependent for their development upon the sex glands and representing the retention and development of characters of the asexual embryonal form.	Body temperature of the male. Mammary gland of the male.	Plumage of the cock. Spurs of the cock. Head furnishings of the hen.
2. Sex characters dependent for their development upon the sex glands.		
(a) Arising through synergistic action of the sex gland.	Penis, Prostate Seminal vesicles and increased body growth of the male. Uterus, mammillæ, mammæ and increased body temperature of the female.	Comb and wattles of the cock. Syrinx of the cock.
(b) Arising through antagonistic action of the sex glands.	Reduction of the Müllerian duct in the male. Reduction of the Wolffian duct, clitoris and slighter body growth of the female.	Plumage of the hen. Absence of spurs in the hen.

[4] See for instance the very important work on the free martin by Lillie (*b*) (*c*) and by Keller and Tandler.

II. Rhythmic Gonadal Function in the Adult Female

Introductory

Ovulation.—*The Associated Ovarian Histological Events.*—The assumption of sexual maturity is associated in the ovary with two histological events which are new to that organ—ovulation and the formation of corpora lutea. We are still entirely in the dark as to the causes which determine this new behavior on the part of certain of the follicles, for instead of undergoing atresia, as in prepubertal life, they continue to grow, turning into the well-known Graafian follicles, in which the egg after undergoing its first maturation division becomes free in a follicular fluid and is expelled from the ovary by follicular rupture. Nor are these processes clearer to us by the statement that the egg dominates the situation (R. Meyer, Schroeder), for we still have to recognize the sudden assumption of vitality on the part of the egg or the removal of some toxic influence which makes it no longer necessary for them to die in the earlier stages of their existence and growth. The literature is filled with similarly indecisive explanations for the act of ovulation itself. Hyperemia of the ovary, the increase of hydrostatic pressure within the follicle and the final tearing of the overlying ovarian tissue (the albuginea and a slight amount of cortical substance) would all appear to be facts. The tear probably occurs merely through the sudden accentuation of changes already well advanced, thereby preventing an adaptive response which so often walls off securely, even if thinly, much larger cysts.

Several anatomical criteria for impending ovulation have been made out—characteristics of the structure of follicles the rupture of which is imminent. These are an increased vascularity of the theca interna, an hypertrophy and appearance of minute globules of fat in the cells of the theca interna and a peculiar activity of these cells is tending to invade the follicle by pushing the basement membrane and granulosa ahead of them so as to cause indippings of the follicular wall, even in spite of the pressure which may be present with distention of the follicular antrum. Finally, the first maturation division and the formation of the first polar body takes place before follicular rupture occurs. When follicular distention is relieved by bursting and the consequent escape of the egg with a small complement of granulosa cells, a collapse and folding of the follicular wall takes place and, more important than this, a change in the structure of the wall, for both thecal envelopes (interna and externa) begin to mingle their structural elements with the granulosa, the boundary separating them previously (the Glashaut or basement membrane) being rapidly obliterated at many points. The hypertrophied internal theca cells are

for a little while still distinguishable from the granulosa elements, but as the latter enlarge in a characteristic way to become converted into *lutein* cells they also appear to partake of similar changes so that it is finally difficult to distinguish the two cell types. From both internal and external theca, fibroblasts grow into and amongst the inner thecal and granulosa cells and sprouting capillaries also keep pace with the enlarging cells, which come finally to fill up the old follicular central space, so that a solid, spherical epithelioid structure is created—the corpus luteum.

Undoubtedly the main mass of the yellow body is constituted by a transformation of the granulosa cells, as was first made out convincingly for the mouse by the classic researches of Sobotta and has been recently apparently confirmed for man by R. Meyer, Wolz, Wallart, Timofeiev, Strakosch, Reusch, Novak, and others. Yet, as we have indicated, the enlarged internal theca cells would appear to form some of the lutein elements (at least at the periphery of the corpus) as Van der Stricht was able to show in the bat and dog and as has again been supported by the studies of Corner on the histogenesis of the corpus in the sow.[5]

The peculiar structure which is thus formed as a successor to the ruptured follicle has specific duties to perform, as has become clearly established through the researches of Ludwig Fränkel.[6] It accomplishes this by pouring into the blood stream an internal secretion, the intimate relations between lutein elements and the capillaries being typically adapted to that end. The corpus luteum has a definite functional life cycle, though it may persist for a long while in the ovary, and it constitutes one of the most important even if transitory endocrin glands. Hormons from the corpus luteum provoke distinctive changes in the remainder of the reproductive and accessory reproductive organs of the body, changes which are intimately connected with the proper provision for the fertilized ovum and the new offspring resulting therefrom.

Conditions in the Mammalia in General.—*Ovulation in Many Mammals Rhythmic.*—In many mammals the events which we have just described occur spontaneously at regularly repeated, fairly short intervals so that we may speak of the ovulation cycle of the species in question. In other cases, as Heape has shown, ovulation happens but once or twice per year, at times presumably when Nature affords the best provision for the

[5] These are the "theca-lutein cells" of Seitz and others, so-called to distinguish them from the chief or granulosa lutein cells.

[6] It is true that Fränkel's formulation of the dependence of menstruation on the corpus luteum in the sense that the former was produced by the latter was erroneous; but the premenstrual endometrium is so produced. He has been sufficiently castigated by many subsequent workers and acknowledged the error of his ways if by no other evidence than by his recent reformulation in the Liepmann Handbuch. This should not cause us to overlook Fränkel's establishment of the connection between the corpus luteum and the uterus both in the cycle and in implantation. The necessary presence of the ovary for menstruation had been demonstrated by the classic transplantation experiments of Halban.

offspring. In these latter animals if fertilization does not result at one of these ovulation periods, a long period of inactivity or rest may result, the period which Heape has termed the anœstrum; on the other hand, it is open to question whether in all cases of animals with shorter cyclic ovulation and when fertilization is prevented, any true resting period, anœstrum or diœstrum, can be said to exist. In some cases of cyclic ovulation a resting period certainly does not exist (e. g., the rat and man), for no sooner does the functional life span of one corpus luteum draw to a close than a new cycle of ovarian and other genital changes is begun.[7]

Œstrus the Precursor of Ovulation in the Mammalia.—Certain bodily changes associated with this cyclic ovarian activity are probably invariably present, are often very pronounced and in some cases are preliminary or anticipatory in time, so that the approaching ovulation may be predicted with certainty. These anticipatory events constitute the phenomena of pro-œstrus and œstrus, knowledge of which we owe above all to the long continued studies of Walter Heape of Cambridge and, more recently, to those of F. H. A. Marshall. Thus animals possessing a cyclic ovulation show a cyclic œstrus and the time of ovulation always occupies a definite position in the so-called œstrous cycle.

Succession of Events in the Œstrous Cycle.—Since the phenomena of pro-œstrus and œstrus are somewhat different in different forms and are completely understood in but few forms, it will be well to give here but a single typical example of the succession of these events in an œstrous cycle. Stockard and Papanicolaou have given us a most admirable and detailed account of cyclic œstrus and ovulation in the guinea pig and Long and Evans have conducted similar long-continued studies on the sequence of events in the rat. To breeders of animals and veterinarians some of these phenomena have long been familiar, for example, the twenty-one day cycle in the cow. Corner has recently furnished details of the events in œstrus in the sow. I shall describe the series of changes in the œstrous cycle of the rat.

Changes in the ovary and essentially the growth and transformation of follicles provoke changes in the entire reproductive tube from the fibrinated end of the oviduct to the external vaginal orifice. We are only beginning to understand these changes in their entirety. Until very recently they were thought to concern the uterus alone. This is probably due to the predominant rôle of uterine changes, causing menstruation, in man and the primates. The tubal changes are still obscure, but it would

[7] In other animals, for example the cat (Longley), ovulation is not spontaneous but is induced by coition and if opportunity for the latter is not afforded, degeneration of the ripe Graafian follicles occurs and corpora lutea are not formed. It is not yet possible, however, to greatly enlarge the list of mammals in this class as Ancel and Bouin have done, for many of their examples have subsequently been proven to constitute ideal examples of the spontaneously ovulating class, e.g., the guinea pig and rat.

appear certain at least that a secretory phase characterizes the epithelial elements of the tube especially in its peripheral or ovarian portion at about the time of and immediately succeeding ovulation though doubtful whether the cells lose their cilia and later acquire the same (Moreau).[8] More remarkable are the changes which occur in the stratified squamous epithelium of the vagina, for here in many animals a great increase in the thickness and differentiation of the cell layers takes place as well as a massive desquamation of the surface sheets of cells. It is by reason of the latter fact and by recognition of the different types of desquamated cells found in the vaginal lumen that in the case of some animals one can accurately subdivide the stages of pro-œstrus and œstrus, as Stockard and Papanicolaou have shown for the guinea pig and Long and Evans for the rat.

The entire œstrous cycle in the rat occupies ninety-six hours, i. e., this is the time interval from one initiation of œstrous changes (i. e., from one pro-œstrus) to the next recurrence of the same phenomena. In the case of this animal it is possible by means of changes in the microscopic makeup of smears from the fluid and cellular content of the vagina to distinguish five different cell pictures. Three of these occur before the time of ovulation and are related to certain peculiarities in the behavior of the animal, permitting us to subdivide the total ante-ovulatory part of the cycle into three periods, the pre-œstrous, œstrous, and postœstrous periods, as shown in Fig. 1.[9] The remaining two of the five components of the cycle, as determined by the study of the smear, occur after ovulation, and these have been combined in the above diagram into one period—the post-ovulatory period.

In pro-œstrus the external genitals begin to show an evident swelling and the cells in the vaginal smear no longer consist of leukocytes with epithelial elements but consist of the latter alone, either singly or in considerable sheets. Histological studies of the vaginal wall disclose the origin of these cells from the surface of a suddenly thickening and differentiating epithelium, which was previously but four cell layers in height but is now double this dimension. Toward the end of this stage the hyperemia which has begun to show in the mucosal folds about the vaginal orifice now involves the uterus, which in addition to its heightened vascularity becomes distended with fluid. Rats will not mate during the pro-œstrus.

The next stage in the œstrous cycle of these small rodents is the œstrous

[8] But see Voinat, Schaffer, Hoehne and Tröscher, as well as the older reports of tubal menstruation recounted by Schaeffer.

[9] It will be noted that I do not follow Hill and O'Donoghue in denying the occurrence of any "postœstrous" and ante-ovulatory period in the eutherian mammals, for ovulation is not immediately consequent upon œstrus in the rat or indeed in several other eutheria known to me.

period proper, which shows itself by the replacement in the vaginal smear of the small, nucleated epithelial cells of the pro-œstrus by large, non-nucleated, transparent, cornified cells. Animals invariably mate during this period, the approximate length of which is twelve hours. During it the uterine hyperemia and distention reach their greatest expression and recede. Large Graafian follicles are by this time found in the ovary and in some instances the first maturation spindle may be formed.

The next, or postœstrous period (eighteen hours in length) is similarly characterized by a continuation and accentuation of the vaginal smear picture of the preceding stage, for the desquamated cornified cells now appear in greater numbers. In the ovary the final ripening changes preliminary to ovulation take place, the first maturation mitosis and in most cases ovulation itself taking place before the end of the period. Immediately consequent upon ovulation the ovarian portion of the oviduct becomes distended with a clear fluid which had previously been secreted into the periovarial space or *bursa ovarica*. In the ovary itself corpora lutea are rapidly formed out of the follicles which have shed their eggs and while for perhaps half a day there is some central follicular cavity not yet closed up or occupied by the new lutein tissue, when one day has transpired this is no longer true and the corpora lutea are apparently completely formed structures.

In the postovulatory period it is the corpora lutea which are responsible for further marked changes which now regularly occur in the genitalia of some other mammals. They produce distinct changes in the rats' mammary gland. The mammary ducts, which show mild growth changes during the ante-ovulatory periods of the œstrous cycle, take on a special activity, branching rapidly, after the incidence of ovulation, so that a considerable complexity of the ducts now results, a complexity which is not resolved by degeneration until after the occurrence of the next succeeding pro-œstrus, more than fifty-four hours afterwards. Thus, cyclic growth and regression changes occur in the mammæ of isolated virginal animals, changes which owe their fullest expression to hormons produced by corpora lutea. In animals in which ovulation is not spontaneous but is produced naturally only by the act of coition, these growth changes in the mammary apparatus do not occur unless ovulation and the consequent corpus formation have resulted. Ancel and Bouin have proven this decisively in the rabbit, where ovulation was induced by permitting copulation with vasectomized males or by puncture of ripe Graafian vesicles. In this animal the formation and function of corpora lutea entail specific pregravid changes in the uterus, changes in the direction of an increase of both muscular and epithelial elements, the latter forming glandular invaginations, changes which are at their height from the seventh to the tenth day and which regress from the fourteenth to twenty-fifth day, in nice correspondence with the degeneration of the corpus

luteum. The French investigators have argued clearly that these pregravid changes are only referable to the ovarian lutein bodies, for the formation of the latter constitutes the only new factor introduced in their experiment. The changes are not due to the eggs because these are unfertilized and soon die, nor are fetal membranes responsible, for these are not formed. Furthermore, nervous or other influences resulting from the act of cohabitation itself cannot be responsible, for the production of corpora by mechanical rupture of follicles leads to the same effect. Keller has similarly described a regular postovulatory uterine hyperplasia in the bitch and Corner in the cow. In the rat, as Long and I have shown, the corpora lutea, when mating is prevented, are so shortlived that marked effects on the structure of the reproductive tube are not produced. Mechanical stimulation of the lower part of the rats' cervical canal, however, a thing which takes place normally in coitus, in some way produces conditions which prolong the functional life of the corpora lutea and when this is the case the latter are able to exert endocrin effects in the form of outspoken changes of structure even in the vagina, changes which consist in the exchange of a stratified squamous for a very high stratified cylindrical epithelium identical with that occurring during pregnancy.

Very definite responses hence occur as a result of the functional activity of the corpora lutea, responses which may be summarized by their designation as the establishment of a pregravid or pseudopregnant condition. This condition is most clearly expressed in the lowest of the mammalia, the marsupials, where very remarkable developments take place. The pouch enlarges and its sweat and sebaceous glands reach a state of development and activity only comparable with that found in pregnant animals. The female starts to clean out her pouch in the same way as does a pregnant one in preparation for the reception of the young. Coincidently mammary hypertrophy is readily palpable, the enlarged glands even being comparable with those found some time after the birth of young. Nor are there lacking uterine changes. The uterine mucosa is hyperemic and thickened, its glands hypertrophied. So evident is the whole condition that the term pseudopregnancy was first applied to the postovulatory condition found in these creatures by Hill and O'Donohue.[10] However, as already intimated, the same phenomena to a varying extent can be found in higher members of the mammalia.

There is thus a regular succession of events in cyclic œstrus in the rat and presumably in any of the cyclic spontaneously ovulating mammals. By reason of these events it is possible in the living animal to predict the time at which the egg cell is expelled from its site of formation in the ovary, completes its second maturation division and undertakes its journey

[10] These very remarkable changes have all been confirmed by the researches of Hartman on the opossum, the early embryology of which has been so authoritatively handled by him (personal communication).

through various portions of the Fallopian tube. We are able to ascertain these facts because of the synchronism of particular events which occur in the ovary and other portions of the reproductive system. This synchronism, or parallelism, between the changes of the ovary and those in the uterus and vagina can be seen at a glance in the following table:

SCHEMATIC OUTLINE OF COORDINATED CHANGES IN OVARY, UTERUS AND VAGINAL SMEAR DURING THE ŒSTROUS CYCLE OF THE RAT

Stage	Vaginal Smear	Uterus	Ovary
Pro-œstrus	Uniform sized, nucleated epithelial cells in great numbers, without admixture with leucocytes or other cells.	Uterus toward end of period becomes distended with fluid.	Preceding corpora lutea have begun to show evidences of fatty degeneration.
Œstrus	Cornified cells only, not in macroscopic abundance.	Uterus reaches greatest hyperemia and distention; regression.	Graafian follicles may undergo maturation.
Postœstrus	Identical with above, and macroscopically very abundant.	Peculiar vacuolar condition of epithelial cells.	Maturation; toward end of period ovulation occurs.
Postovulatory	During first 6 hours many polymorphonuclear leucocytes together with cornified cells; then the latter disappear and small, nucleated epithelial cells take their place together with the leucocytes.		Young corpora lutea; eggs in oviduct.

Conditions in Man.—A. *Menstruation and the Endometrial Cycle.*—Although for a very long time it has been felt that menstruation stood in some definite relation to ovulation, it is only within the last few years that anything like rigorous proof of the necessary connection of the two phenomena has been obtained. The study of menstruation itself, which is by no means complete, would still appear to bear traces of the conceptions of mysticism and folk-lore with which it was invested by primitive people (E. Novak (*f*)). It is also possible to find in the more serious current scientific literature attempts to relate the twenty-eighth day recurrence of this phenomenon in women with effects of the moon (Arrhenius, Schatz), or with the old Hippocratic theory of a periodic cleansing or detoxification of the body as, for instance, in the statement that when certain flowers—particularly anemones—are held in the hands of a menstruating woman they rapidly fade out and die, due to the presence of a toxin in the

sweat (Schick).[11] It is indeed surprising that exact anatomical information about menstruation is so recent and that the conception of insignificant tissue loss formulated by Gebhardt (*a*) and accepted by Schaeffer, lasted as late as 1908, when the famous paper of Hitschmann and Adler first gave us the truth about the endometrial cycle.

Due largely to the latter observers and to the subsequent work of Robert Schroeder, we now know that the menstrual processes may be defined as the desquamation of the superficial or "functional" layer of the uterine endometrium, the layer which constitutes from three-fourths to four-fifths of its depth, the remaining portion of the mucosa, the basalis, possessing a thicker-meshed stroma and the ends of the uterine glands,

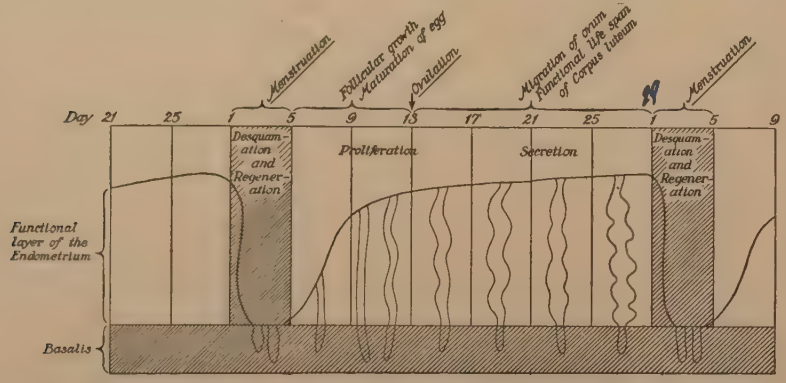

Fig. 1. Scheme of the menstrual cycle (slightly modified from Schroeder).

regeneration from which furnishes the epithelial reinvestiture of the naked wound.

The essential note, however, furnished by these newer studies on the endometrium does not merely concern menstruation itself but the conception of cyclic structural changes undergone by the uterine mucosa. The diagram in Fig. 1, which is slightly altered from Schroeder, will demonstrate these changes, the curve representing the surface of the mucosa and the base line, the outer limits of the endometrium or the position of the muscle layer upon which it rests. By consulting it one sees that a very rapid reinstatement occurs after the menstrual denudation, so that on the ninth day of the cycle the greater part of the endometrium has been re-established, though a slower growth continues to occur. In the latter phases of the cycle the uterine glands, which are also schematically drawn,

[11] The idea of the existence of a menstrual intoxication ought not, of course, to be mentioned so casually. There is a very considerable literature here. Many generally distributed body changes are referred to this. Aschner regards a menstrual enlargement of the liver and spleen as evidence of a periodic toxemia. The menstrual necrosis of the endometrium itself has been viewed as a localized auto-intoxication, the school of Gautier viewing this as due to the accumulation of arsenic by the endometrium (cf. Gautier, Ries, Imchanitzky-Ries and Frommer but also Schroeder, Arch. f. Gynäk., Bd. 104).

show both hyperplasia and hypertrophy of their epithelial elements, so that during the end of the cycle the glands are thrown into kinks or folds and possess a corkscrew appearance. The glands not only show this great increase in their epithelial elements but also a marked functional activity of the latter as shown by the accumulation of glycogen, fat, lipoids and mucus in their high, cylindrical cells (Ascheim, Wegelin, Driessen, Schroeder, Meyer). These epithelial changes in the uterine glands have been accompanied by changes in the stroma cells, which are also larger and in the middle layers of the endometrium (the so-called spongiosa) are separated by an edematous distention, anastomosing with one another by processes. These enlarged cells of the tunica propria or endometrial stroma look like young decidua cells, and indeed, only slightly more pronounced changes would enable them to be termed such. The endometrium

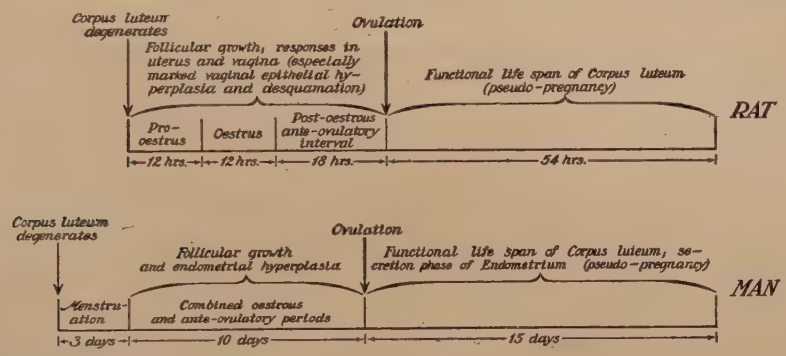

Fig. 2. Schemata designed to show a comparison of the cyclic œserous cycle of some mammalia and the human menstrual cycle.

at the end of the cycle is hence well termed—a "pre-gravid" structure and its changes viewed as a contrivance to facilitate implantation.[12] According to Schroeder, the beginning of *secretory* function on the part of the epithelial cells of the glands occurs at about the thirteenth to fifteenth day of the menstrual cycle and is first indicated by the appearance of a clear zone in the basal part of the cell, the nucleus being pushed a little toward the lumen.

It is of interest that before the discovery of the endometrial cycle any or all of these cyclic transformations in the uterine mucosa were looked upon as pathological. Not the least aspect of the contribution by Hitschmann and Adler was its immediate demonstration, for instance, that the so-called *endometritis glandularis hyperplastica* of Ruge was the normal premenstrual mucosa, that the *endometritis exfoliativa* was the status ante

[12] Fraenkel has proven the necessity of corpora lutea for implantation. Leo Loeb has made the important discovery that foreign bodies will produce uterine tumors which are astonishing simulations of the maternal placenta and that such responses are dependent on the presence of the corpora lutea, a fact which Corner and Warren and Long and I have been able to abundantly confirm in the rat.

and intra desquamationem. The recent diagnoses of endometritis, and especially of the so-called interstitial endometritis, have employed as criteria the abnormal presence of polymorphonuclear leukocytes, of lymphocytes and of plasma cells (cf. Schönberg, Mönch) and Schroeder has shown how serious such infections may be without obliterating the cyclic anatomy.

B. *Time of Ovulation.*—Three means of study could be employed, and as a matter of fact have been employed, in the determination of the time of ovulation in man. First, the study of the exact histological conditions in the uterus and ovary at various times in the menstrual cycle and, especially, the detection of the approximate time of ovulation by the discovery of mature Graafian follicles or of very young corpora lutea which are still in the proliferative stage. Second, the determination of the "conception optimum" in pregnancies following a single copulation, it being taken for granted that this means the determination of the time of ovulation since a very limited survival of either ova or sperm is postulated. Third, the determination of the age of early human embryos which may be referred to a single copulation and hence the determination of the time of ovulation, the same postulations being made.

We may discuss briefly the results obtained by these three methods of study. The method of anatomical study of the ovaries has, as far as naked eye inspection of the ovaries is concerned, been carried out by Fraenkel, Villemin, Witas, Halban, Köhler, Delporte and others. These investigators disagree among themselves, Fraenkel,[13] for instance, finding "fresh" corpora lutea rather late in the period (eighteenth to nineteenth day), Delporte at the time of menstruation. As Ruge II and R. Meyer have emphasized, so simple a method, even if carried out with the greatest care (as it must be admitted Fraenkel has done), is quite inadequate for this task, for deeply seated corpora lutea are notoriously easy to overlook nor can the age of a corpus be estimated with the naked eye. It is obvious that to be decisive, histological serial study of both ovaries should be undertaken and the material should be obtained from cases with a reliable and regular menstrual anamnesis, the supposed period of the cycle being confirmed by histological study of the endometrium. Few, if any, studies with such comprehensive material and such criteria have been carried out. R. Meyer and Ruge II have perhaps made the nearest approach to this while careful histological studies have also been made by Schroeder. These painstaking, not to say preëminent students of the subject do not agree among themselves, Schroeder claiming a mid-interval follicular rupture (fourteenth to sixteenth day) while the Berlin observers place a date early in the second week as the usual ovulation time. This disagreement, how-

[13] Fraenkel's latest results are summarized by Fr. Tschirdewhan. In somewhat over three hundred laparotomies forty cases of "fresh corpora lutea" were detected by the method of inspection. Ninety per cent of these occurred later than the mid-intermenstruum and over half occurred from the eighteenth to twenty-sixth day.

ever, may be regarded as minor. It is interesting, furthermore, that the work of all of these investigators (Fraenkel, Ruge, Meyer, etc.) indicates the occurrence of fresh corpora and consequently of ovulation at any postmenstrual time up to the close of the third week.

During the war, German gynecologists (Siegel, Pryll, Jaeger, Nurnberger, Zangmeister) recognized the unusual opportunity to study the incidence and length of pregnancies which could be dated from a single copulation—in these instances pregnancies resulting from cohabitation during very short military furloughs of the husbands. These studies have shown that the majority of such conceptions occur in the first portion of the cycle, Siegel claiming that fifty-two per cent of them occur in the interval from the sixth to the twelfth day.[14] This corresponds nicely with the average time of ovulation according to the histological researches of Meyer and Ruge and would tend to show that in man, as in other mammalia, the time of fruitful cohabitation coincides with that of ovulation, showing a short life-span of the free ripe male or female sex elements. Here again, however, it must be admitted that the conception data show clearly that pregnancy may follow coitus at any time in the cycle, for example, even on the very last day of the cycle, the expected menses being prevented.

The third method of determination of the time of ovulation consists in comparing the exact development of very young human embryos of known copulation age. In the mammalia, embryos of the same copulation age show a remarkable uniformity in development so that we would be obliged from this alone to assume a rather constant time for ovulation, fertilization, tubal journey and implantation as well as development even if all these phenomena were not independently determinable by anatomical study. Triepel, Grosser and Mall have argued with great force that we should be slow to postulate a radical difference for man. If the time of ovulation varied as widely as some of the foregoing statistics would seem to demand, then this alone is probably the greatest variant in the whole series of processes in early embryonic stages. If marked variations were found in the degree of development of embryos of the same copulation age then it would be logical to postulate variation in ovulation, fertilization, tubal journey or the speed of development. If such variation does not appear, then we can justifiably look upon the ovulation time (which probably conditions fertilization) as constant. Furthermore, if embryos of the same copulation age show essentially similar development, regardless of the particular time of occurrence of coitus in the menstrual cycle, the facts could hardly be explained by the assumption that the time of ovulation in such pregnancies occupies a constant relation to the menstrual cycle, but

[14] But see here Pryll, Jaeger, Nurnberger and Ruge, the last of whom has collected all the cases previously reported and reports 24 per cent of such conceptions occurring from the first to the ninth day and 26 per cent from the tenth to fourteenth day.

only by the assumption that it is constantly related to the cohabitation act, that it is in fact almost coincident with it. The method of study of the degree of development of young embryos is therefore well calculated to disclose whether a standard or variable time of ovulation can be said to exist. Grosser, Triepel, Mall and Zangemeister have examined with this special point in view all early human embryos where the time of cohabitation was supposedly known. Unfortunately, the data are fragmentary and inharmonious. Such as the evidence is, however, it tends to stress one of the points established by the study of war pregnancies, that is, that ovulation can occur on almost any day of the menstrual cycle. Only five or six cases of undoubtedly reliable history probably exist and it is obvious that these are too few for us to parallel with the data on the "conception optimum." We may expect that sufficient and unimpeachable data will eventually enable us to substantiate the statement made by Mall, who felt that the embryological data even now support and will support the "conception optimum" data on ovulation being usually early in the intermenstruum and thus will furnish another check on our notion that this is the normal time of ovulation as we have seen by direct study of the ovary.[15]

C. *Chronological Relations of Menstruation and Ovulation and Comparison of the Menstrual and Œstrous Cycle.*—We may thus regard the researches upon human ovulation as tending more and more convincingly to show this act to take place normally somewhat before the middle of the menstrual cycle (the menstrual cycle being regarded as the complete time interval from the first appearance of one menstrual hemorrhage to the next). In Fig. 1 the time of ovulation is thus approximately or diagrammatically placed. The newer studies on the uterine mucosa and the chronological relations between the time of ovulation and menstruation now enable us to have a more intelligible conception of the interrelation of uterus and ovary in man, an interrelation which we have already seen to be fundamental in the other mammalia. During the preovulatory phase of the menstrual cycle the lining of the uterus, which has been almost denuded by menstruation, does not merely repair itself but undertakes

[15] As to the quandary in which we are placed by the recognition of irregular, i.e. very early or very late, ovulation, two attempts at explanation have been made. Robert Meyer claims that the exact time of follicular rupture is indeed open to considerable variation but that the maturation of the ovum and lutein change of the granulosa cells is less variable. The proof of this contention is not yet at hand. Triepel has advanced the idea that, though a normal time for spontaneous ovulation exists, coitus may precipitate this or induce another ovulation. Were this true, infertile coitus should thus greatly disturb the menstrual rhythm and it does not do so. Furthermore, Triepel's hypothesis, as he admits, calls for the presence of large follicles or other favorable ovarian conditions at any time in the cycle. The variation in the time of ovulation, while apparently proven, is thus difficult to explain and perhaps can only be harmonized with the growing body of evidence which points to a standard time of ovulation by the view that most of such variations occur in single coitus pregnancies, where a condition of relative sexual abstinence might be conceived as favoring the idea of an unusual response—the induction of ovulation—as a cohabitation effect.

vigorous and extensive growth. It would appear that these growth changes are due to the liberation of hormones from the ovary, since much growth does not take place on ablation of the ovaries or in conditions of hypo-ovarism. As far as we know, the most active ovarian tissue at this time in the cycle is represented by the growing follicles. These, as we have seen, are in the other mammalia also associated with certain growth changes in the reproductive tube during the periods of pre-œstrus, œstrus and postœstrus.[16] Ovulation and the production of the corpus luteum can also be said to exert a specific effect upon the endometrium for corpus hormones would seem definitely responsible not merely for the further growth of the endometrium to its premenstrual height but also for the assumption of the function of secretion on the part of the uterine glands. We have already said that Schroeder has discovered this to be evident as early as the thirteenth day, so that the correspondence with ovulation is quite close.[17]

The so-called premenstrual endometrium, therefore, while with characteristics more pronounced near the end of the menstrual period, is nevertheless the resultant of a gradual transformation which has been taking place from the moment when the corpus luteum was produced in the ovary through follicular rupture, and it may rightly be regarded as a product of the activity of that ovarian structure. Furthermore, the recent work of Marcotty, Miller and R. Meyer has shown a beginning fatty degeneration of the corpus of the preceding ovulation in man at the time of onset of menstruation. A new, and it would appear a sound, interpretation of menstruation is furnished by these facts. Menstruation may be regarded as the degeneration of uterine tissue which has been built up and specifically nourished by hormones from the corpus luteum, hormones which have been suddenly withdrawn on the degeneration of the corpus. In other mammalia (e. g., the rabbit) we have seen that rather extensive uterine changes are also produced by the corpus, but in these cases it would appear that on the death of the corpus or diminution of its activity there is a slower and gradual resorption of the accessory uterine tissues. Apparently only in man and the primates is this uterine degeneration "stormy," i. e., so sudden that an extensive wound is produced which must

[16] It is true that Marshall and Runcimann have challenged the specific idea that hormones from the expanding follicles are responsible for bringing on heat, for their premature rupture of these follicles and consequent artificial production of corpora lutea in bitches at a time preceding an expected œstrus did not delay the latter. Their results are open to criticism. Proof that all of the follicles in question were found and ruptured is difficult or impossible to deduce. Sonnenberg (see also Marshall (*b*), Phil. Trans., 1903, B 196 and Marshall and Jolly, same, B 198) has reported the artificial production of heat in animals by the subcutaneous injection of the *liquor folliculi* from other animals which were in heat.

[17] It is in fact probable that the corpus luteum must be several days old in order to exert this effect and it is probable that in my diagram ovulation should be shifted still further forward and in front of Schroeder's calculations to a greater extent than I have done; possibly the ninth or tenth day of the cycle would have been preferable.

be healed over. In some of the mammals with cyclic œstrus, and as Long and I have seen to be the case in the rat, a similar beginning fatty degeneration of the corpus luteum is coincident with the new œstrus cycle so that we may also view the same event as inaugurating the cycle in man. In the latter case, however, uterine growth changes cannot be immediately produced, for the first part of the new cycle is occupied by the degeneration and removal of old tissues produced by action of the corpus formed in the preceding cycle. Only when this necrosis is complete and the tissue débris removed can the endometrium again begin its cyclic growth.[18]

It does not need to be emphasized that these newer considerations necessarily lead us to abandon the terminology and, what is more important, the concepts which have previously existed in the literature on menstruation. The endometrial changes should be not be designated *premenstrual,* for they are obviously not formed in order to necrose; they are more properly termed *pregravid.* Nor can we speak of menstruation as a normal process or as a "menstrual mechanism." The whole mechanism of these changes in the reproductive tract is gauged for another event, i. e., pregnancy, and menstruation represents the failure of this contrivance and is more properly viewed as a pathological event. Furthermore, our knowledge that menstruation does not occur when a corpus luteum is functional either in the normal cycle or, for example, during pregnancy should not lead us to the conception of Seitz and Wintz, Kohler and Halban, Reusch, and others, who speak of the "menstruation repressing" action of the corpus. The former observers believe they allay uterine hemorrhage by the administration of certain lutein extracts and the latter explain the

[18] The reader will have seen that the comparison between menstrual and œstrous cycles which we have instituted conceives of menstruation only as the beginning of a new sexual cycle because it is precipitated by degeneration of the corpus luteum. But our concept also regards menstruation as a special interpolated event peculiar to man and possibly to primates. It is a degenerative change. We would hence view it as fallacious to compare menstrual bleeding with the pro-œstrous bleeding of the bitch which comes from hyperemia and is a concomitant of growth, not degeneration. It is equally fallacious to regard the œstrous vaginal desquamation of rodents as comparable to menstruation. This itself follows sudden growth changes in the vagina precipitated by corpus decay and such growth changes are characteristic generally of pro-œstrus and œstrus. Thus growth in the rat's mammary gland is inaugurated before ovulation (Sutter). The simple conception that the vaginal lining as well as uterine is protected by the corpus and degenerates on corpus impairment—as Stockard and Papanicolaou infer—cannot be accepted. Nor can we follow these writers—whose work has otherwise marked so significant an advance in our knowledge of this subject—in their statement, "A secretion elaborated in the ovary apparently by the corpus luteum is necessary for the normal development and persistence of the uterine and vaginal mucosa." Only special growth changes (the œstrous and the pregravid changes, or as we have termed them, pre-ovulatory and postovulatory ovarian effects) are referable to the periodic function of the gonad—not the actual existence of these mucous membranes themselves. Their view of corpus luteum essentially would leave unexplained the actual growth and differentiation of the genitalia in the presence of the prepubertal corpus-free gonad and also the integrity of the genitalia in animals which have only one œstrous season per year and a very long time interval after corpus decay; furthermore, such a view would not explain the first œstrous vaginal changes in rats—changes which could not result from a degeneration due to corpus decay for no corpus has previously existed.

incidence of premature menses which can be produced by radiation or ablation of the ovaries as due to the removal of the menstrual repression exercised by the corpus. As long as the corpus is functional it continues its specific "nourishment" of the endometrium;[19] and when it degenerates or is injured or removed the latter structure must die. It is consequently, as Meyer urges, no more correct to look upon the corpus as existing to repress menstruation than to consider the conveyance of nourishment to a living being as the repression of death instead of the conservation of life. It is quite apparent why the uterine hemorrhage which occurs within two or three days after extirpation or radiation of the ovary would normally happen only after the operation had been done in the second half of the menstrual cycle, as Seitz and Wintz have proven. Before that time the functional or menstrual part of the endometrium has not been developed, for this is dependent upon the function of the corpus luteum which has not yet come into being or has barely been formed.

Our present knowledge, on the other hand, firmly supports the conception that functional corpora lutea do repress the further growth of ovarian follicles and that their removal initiates a new cycle by permitting follicular growth to take place.[20]

From the above considerations it is evident that no menstruation can occur without a preceding ovulation and that the first menstrual blood flow is incident upon the degeneration of the preceding and first corpus luteum produced after the first ovulation. It is also clear why women in the lactating period, or even after other amenorrheas due to ovarian hypofunction, may conceive (and hence ovulate) without menstruating. Furthermore, the old discussion as to whether in pregnancy the fertilized egg belongs to the last normal or the first missed menstrual period was due to the erroneous conception of the concurrence of ovulation and menstruation. Menstruation is always the terminal destruction of effects produced by a preceding ovulation and its corpus luteum so that the fertilized ovum belongs to the first missed menstruation, i. e., to the ovulation preceding it,

[19] This is elegantly shown by the fact that placentomata may be produced in the rat's uterus (as Long and I have shown), during the time of lactation, when without this special stimulus the uterus normally undergoes a "lactation atrophy."

[20] Stockard and Papanicolaou have thus hastened the occurrence of a new œstrous cycle in the guinea pig by ablation of the corpora lutea. Most convincing and of great scientific importance are the procedures of veterinarians, who by manual palpatory methods *express* a persistent corpus luteum in cows which do not come in heat. The artificially aroused œstrous is even said to appear in 50 per cent of all cases on the evening of the third day or morning of the fourth and at all events in about 80 per cent of the cases within the next four weeks. Zschokke and Hess especially have emphasized the value of this operation, which is done both per rectum and per vaginam. It would appear to have originated through the procedure of Zangger, who was the first to call attention to cystic degeneration of ovaries in cattle failing to come in heat and first practiced manual rupture of the ovarian cysts by way of the rectum. At about the same time Zangger did his work Villiger introduced the enucleation of the corpus luteum in the same way. Then Hegelund, Zschokke, Hess, Nielson, and Poulsen employed and expounded it for the induction of œstrus. The procedure is also used with other aims, e.g., in retained desiccated fetus, pyometra, etc.

this ovulation, however, having occurred at a very considerable time interval before the expected menstruation.[21] Mall and Triepel have shown that in cases with a reliable history the copulation age of embryos is always about ten days less than the menstrual age, which is the term used for the time elapsing from the last normal period.

There are thus fundamental analogies between the sex cycle of the other mammalia and of man, although in man an œstrous period cannot properly be said to exist nor can a true menstruation be said to occur in the other mammalia. In both cases certain ante-ovulatory ovarian changes —probably the ripening follicles—are clearly associated with certain other changes in the reproductive system and, again, in both cases certain postovulatory ovarian changes—the production of corpora lutea—are associated with certain further changes in the reproductive system. We have thus to recognize not only that there is a primary rôle of the gonad in the cyclic change of the genitalia but that specific tissue components of the ovary produce specific effects on the genitalia.[22] In this field, furthermore, as in so many others, the study of certain pathological states serves to strengthen the physiological conceptions which have been expressed

[21] This resolves the extensive discussions on this subject, which were participated in by Kundrat and Engelmann, Siegmund, Loewenhardt and Reichert, all of whom claimed that the fertilized egg "belonged" to the last normal menses and which led Aveling in 1874 to give the first true interpretation of premenstrual swelling as pregravid or implantation changes. Furthermore, although at the time he wrote few early human embryos had been well investigated, Ahfeld was inclined to adopt the above views, since the youngest "ova" known to him led him to declare that implantation had taken place by the time of the first missed period and so the ovum could not belong to it. This view of the time of implantation has been supported by the study of very early gestations in the last few years (Peters, Bryce and Teacher), but it cannot lead us to declare that the development of the embryo was inaugurated quite so early as coincidentally with the last normal period.

[22] The reader will observe that I have been unable to follow Schroeder, Aschner and especially R. Meyer in the complete extent to which they ascribe all changes in the ovary to the egg alone (see, for instance, R. Meyer: "Das Ei in seinem Reifwerden seinem Reifsein und seinem Tod beherrscht das ganze genitalgeschehen."). According to Meyer, corpus luteum formation begins even in the intact follicle when the egg ripening has reached a certain stage and hence quite regardless of follicular rupture. Furthermore, he believes that the life of the corpus is also dependent upon the life of the egg and that the former structure does not degenerate until the death of the latter. Ruge, Seitz, Grosser and others have already challenged this idea, expressing their belief that the human fertilized ovum cannot be regarded as living almost two weeks after ovulation. Our more exact acquaintance with the conditions in some of the mammalia would also seem to very clearly negate Meyer's contention. Lams and Doorme have recognized an early time of degeneration of the tubal eggs in the case of the guinea pig and the same is true for the white rat. The corpora lutea certainly outlast the eggs and hence deserve to be regarded as possessing an independent normal life span. The extent to which Meyer has pushed his theory would appear consequently unjustifiable, but there is equally no doubt but that if the eggs be fertilized there exists an hormonal effect (Fernwirkung) resulting therefrom, whether by way of the corpus or not, for the so-called pregravid endometrium immediately becomes a gravid one and even an immediately impending menstruation necrosis is prevented. As we have previously shown, the studies of war pregnancies have proven this.

But we are acquainted with circumstances which prolong the life of a corpus luteum other than those which could be contributed by the egg. A good example of this is furnished by lactation. There is a prolonged function of the corpora lutea

above. In grave impairment of ovarian function so that follicular growth does not even take place, the endometrium as seen by curettage samples may not grow appreciably above a mere healing over of the basalis.[23] The stimulus due to substances supplied by the growing and ripening follicles is apparently absent. It is self-evident that the further effects of functional corpora lutea cannot exist. Furthermore, in other cases, it is possible to have the stimulus from ripening follicles in an exaggerated form and great endometrial growth, but since follicular rupture does not take place, none of the peculiar endometrial changes due to a corpus luteum can occur. (In *metropathia hemorrhagica,* for which see below.)

III. True Disturbances of Gonadal Rhythm Which Are Associated with Menstrual Aberrations

If the view which we have developed in the above is correct, it will be apparent that any grave impairment of the ovary must lead to disturbances and eventually obliteration of the menstrual rhythm. The intact menstrual rhythm, then, may be taken as a true indication of ovarian periodicity. On the other hand various complicating circumstances prevent us from immediately assigning menstrual aberration to ovarian deficiency. Even in the presence of ovulating gonads, local trouble with the uterus or lower portion of the generative tract may either gravely disturb the endometrial cycle or irregular hemorrhage may obscure the periodic bleedings so that we are not led to realize that along with the uterine pathology the cyclic mucosal changes are nevertheless going on. These apparent disturbances of menstruation unassociated with ovarian dysfunction fall into two categories—(1) the seeming absence of uterine bleedings on account of mechanical obstructions (which may, for example, cause hematokolpos) and (2) the great increase and irregularity of such bleedings, which may result from uterine polyps, and submucous myomata and from corpus, cervix, portio or vaginal carcinomata as well as from severe endometritis.

Before mentioning the instances of true ovarian disorder which cause disturbances of the menstrual rhythm we may comment briefly upon *ovarian hyperfunction.* The indications of overactivity of the ovary are not at present satisfactorily understood. It is easy to understand that excessive activity of the corpus luteum would conceivably increase the amount of the pregravid endometrial changes and hence the amount of menstrual

which result from the spontaneous postpartum ovulation in the lactating rat, and which have been described by Long and me and designated *corpora lutea lactationis.* We have also indicated that the same prolongation of the life of corpora takes place after infertile coitus which thus delays the next œstrus, and in these instances the unfertilized ova degenerates at the usual time in the proximal portions of the tube.

[23] See for instance the low postmenstrual mucosa reported by Pock, Höfstatter and others in the cases of ovarian hypofunction constituted by war amenorrheas.

necrosis and bleeding. Hence some menorrhagias may be referred to this cause, though it is commonly believed that in such conditions increased contractile power of the myometrium would prevent excessive bleeding. There are known to us two conditions which are apparently associated with ovarian hyperfunction. In neither case (on account of our ignorance of the interrelationships of the endocrin glands) do we know whether the ovarian function is primary or induced. I refer to osteomalacia, where Röntgen or surgical sterilization has a clearly curative effect, and to the idiopathic condition known as true pubertas præcox.

1. Disturbances Producing Amenorrhea.—*Ovarian hypofunction* usually expresses itself by scanty menstruation (oligomenorrhea), too frequent menstruation (polymenorrhea) and by a final cessation of the menstrual function (amenorrhea). It is true that while true amenorrhea is always associated with lack of function of the ovaries, the ovarian disorder can be either primary or secondary. In the latter case it may be invoked by many other conditions so that we are not at liberty to at once draw the inference of gonadal deficiency and institute a therapy directed toward that end. But the new viewpoint of the primacy of the gonads does not permit us in either case to interpret menstrual cessation as uterine trouble. It makes much of the lore concerning amenorrhea treatment and especially the use of "emmenagogues" now appears to us as useless. Just as the etiology of amenorrhea is to be found in ovarian dysfunction, either primary or secondary, so is the cure of it to be sought in a restoration of the gonads either by direct or by indirect procedures and not by attention to the uterus.

A. *Primary Ovarian Involvement.*—When amenorrhea is due to primary ovarian involvement [24] we are usually able to discover:

1. *Congenital hypoplasia* of the reproductive system;

2. The cessation of ovarian function is due to a peculiar degeneration of its follicular apparatus—the so-called *small cystic degeneration* of the ovary. Based on its etiology it is difficult to give this ovarian disorder its proper place. The secondary nature of this disease may be demonstrated by its occurrence in various other affections which in turn have injured the ovary, but there are other instances in which it appears to exist as a condition *sui generis*. Fränkel has given an excellent description of such cases. It is perhaps only fair to say that we are entirely in the dark as to the cause of this aberrant behavior of the follicles, which some view as having been stimulated to begin ovulation in great numbers but to have been overtaken by a cystic transformation before they can

[24] It would hardly seem necessary here to comment upon the physiological cases of amenorrhea or lack of menses. This, of course, occurs in the prepubertal time but also during the period of sexual life in pregnancy and through at least the early part of lactation. In both of the latter instances ovarian activity is manifested through long continued function of the corpus luteum which always depresses follicular growth and the recurrence of new cycles.

mature. This view of the matter might actually assign the disease to an effort at hyper- rather than hypofunction of the gland, and Fränkel's opinion that it is referable to sexual stimulation through nervous influences would coincide with this.

3. *Corpus Luteum Persistens* (Halban and Kohler).—The three cardinal symptoms of the condition which has received this name, namely, (1) amenorrhea, (2) the presence of a hypertrophic and true secreting or pregravid endometrium, and (3) the presence of a functional corpus luteum resembling that of pregnancy, has led to its designation as occult or apparent pregnancy. Several cases of this interesting condition have been reported. If a curettage is done during the late amenorrheic stage the endometrium presents the characteristics of an early decidua, but if this procedure is not carried out an intensified menstruation may ultimately close the amenorrheic pause. The picture corresponds in its entirety to that of an early pregnancy, but the place of implantation of the ovum has escaped all observers, even the most painstaking ones. Rokitansky first saw such a condition, and his careful scrutiny did not discern the implanted ovum either intra- or extragenitally. Ruge I has described such a case, and R. Meyer sectioned serially two cases of tubes and uterus without locating the ovum. Halban's cases, in which the corpus was cystic, apparently belong here, but there would not seem to be any special significance in the cystic condition of the corpus, for this is fairly frequent in the case of the human corpus luteum without the symptom complex which we have just described.

B. Secondary Ovarian Impairment.—Though in many serious genital affections (e. g., malignant tumors, chronic pelvic inflammatory disease) the ovarian function may not be seriously disturbed, yet the gonads are particularly sensitive to some disturbances in the general health and have a particular dependence on other glands of internal secretion. Both the general and particular relations of the ovaries are only beginning to be understood.

1. *Endocrin Upsets.*—The ovaries appear to maintain definite relations with the pineal, thymus and adrenal glands, as well as with the thyroid and hypophysis. We do not propose to discuss this field.[25] Ovarian hypofunction or complete amenorrhea occurs in acquired or congenital hypothyroidism and in that hypophyseal upset which gives Fröhlich's syndrome—distrophia adiposogenitalis. Well known is both a castration and pregnancy hypertrophy of the hypophysis while the thyroid is enlarged both at the menses and in gestation. May the future enlighten us!

2. *Trophic disturbances* of the ovaries produced by general bodily or constitutional upsets are well known.

Hygienic changes have long been known as operative here. Here may

[25] Which in spite of the strictures of Fehling has received a valuable and suggestive formulation in the Aschner monograph.

belong the amenorrhea which Europeans writers have cited as exhibited in girls of the servant class when entrance upon duties in a large city entails sudden alteration of previous rural surroundings. The causes, of course, may possibly be nervous.

The relation of nutrition to ovarian hypofunction has been equally clear, but studies of the particular nutritional components or proportions which are necessary for the gonads remain to be carried out. The Great War would appear to have furnished in the central empires widespread examples of the nutritive impairment of the gonads in the so-called war amenorrheas (see Ebeler). Quantitative under-nutrition expresses itself quickly upon the ovary of the guinea pig (Papanicolaou and Stockard) and upon that of the rat (as I have been able to determine with K. J. Scott), as seen in delayed appearance of the next œstrus.

3. *Systemic diseases,* while frequently involving the ovaries, in some cases have appeared to have special relations to them. One may mention here above all the chlorosis of young girls and tuberculosis. Incipiency in the latter infection may sometimes first be surmised by the amenorrhea. The chlorotic conditions are in harmony with the effect of other acute or chronic anemias, where amenorrhea is extremely frequent. Other infections, though without this peculiar emphasis, take their toll of the ovaries. Here are to be mentioned scarlet fever and typhoid, chronic nephritis and diabetes. The metabolic disorder known as adiposity is also particularly prone to lead to cessation of ovarian function.

4. *Drugs.*—The ovary is particularly sensitive to many chronic and some acute poisons. In the former category belong morphin and to a lesser extent alcohol. Olshausen has described an ovarian toxicity of phenacetin, though this is temporary in effect. Radioactive substances have a highly specific toxic effect upon the eggs and follicular apparatus of the ovary and Röntgen or radium therapy has become the sovereign method of ablation of this function in many cases which were previously submitted to the knife.

5. *Causes of ovarian impairment unknown in their exact mode of operation* are also well known. One must cite here amenorrhea due to nervous origin, particularly to depression and long continued anxiety. It has long been known that severe and sudden psychic agitation may prematurely provoke or postpone an expected menses. But though the nervous connections of the ovary are being continually investigated (e. g., the recent work of Wallart and Dahl), we are actually unaware of the mechanism of nervous control of this organ. Dahlmann and Ricker look upon menstruation itself as a vasomotor paralysis, and various but inconclusive tests of the state of the vegetative nervous system during the menstrual cycle have been made by Franke, Dahlmann and others. Claims are to the effect that both vagotonic and sympathicotonic symptoms are found. Urinary fistulæ predispose to amenorrhea in a way unknown to us; idio-

pathic mammary hypertrophy often has cessation of the menses as a concomitant symptom.

Ovarian therapy in amenorrhea (which, as we have indicated, has a rationale which cannot be ascribed to uterine treatment for this symptom) is nevertheless embarrassed by our inability to affect the ovary except by general methods—hygienic regimen, local stimulus (hyperemia by means of the applications of heat, drugs such as yohimbin, etc.). It is possible that mild dosage with ultra violet rays could prove stimulating instead of toxic in its effect and more than likely that an improved organotherapy with ovarian substance itself, with placenta (Aschner), or with other endocrin hormones will represent therapeutic conquests of the future.

2. Disturbances Producing Uterine Hemorrhages.—In no other respect is the concept which has been developed above of the primary relation of the ovary to the uterus more important than in our understanding of the etiology of certain profuse or irregular uterine bleedings. Since many of these occur at or near the time of menopause, sterilization is a justifiable procedure and it is of significant scientific import that a sovereign method of control of many such hemorrhages exists in Röntgen dosage of the ovaries. This has been so well recognized that this treatment has been indulged in and will probably unfortunately continue to be resorted to without the previous investigation of all aspects of the particular disorder, e. g., hemorrhage from malignant disease will be so treated. Common among the metrorrhagias, however, occurs a disease to which Schroeder has particularly called our attention and for which he has adopted Pankow's term *metropathia hemorrhagica* and which is designated by some (e. g., Novak) "functional uterine bleeding." This affection, which causes a large proportion of otherwise unexplainable irregular bleedings at the time of the menopause and to a lesser extent at puberty, is associated with a definite anatomical and functional condition of the ovaries, a condition which stands in etiological relationship to the uterine disorder. The three cardinal symptoms of metropathia hemorrhagica are: (1) chronic bleeding without reference to the cycle and frequently occurring after a period of amenorrhea;[26] (2) the existence of a large velvety or hyperplastic endometrium as seen in curettage samples, an endometrium which in spite of its thickness does not show the functional changes characteristic for instance of the pregravid structure; (3) the absence of recent ovulation in the ovary and hence of all recent corpora lutea but the persistence of large and apparently ripe follicles possessing healthy eggs and granulosa.

The idea that we may have an ovarian etiology for pathological conditions of the endometrium is not new. The endometrium in this disease has previously undoubtedly often gone under Olshausen's name, *endo-*

[26] Novak, however, describes the hemorrhages as usually menorrhagias although he recognizes that the cycle may be disturbed.

metritis fungosa, or *endometritis cystica polyposa,* and may also have been confused with the normal premenstrual or pregravid endometrium which, as is well known, was also previously looked upon as a hyperplastic endometritis. It differs from this, however, in possessing no signs of glandular "function" (i. e., no glycogen or fat storage or mucus secretion) as R. Schroeder and O. Frankl have shown. Olshausen, Swiecicki, von Winckel and Brennecke ascribed an ovarian cause for this anomaly of the uterine mucosa without, however, discovering the particular type of ovarian dysfunction. Brennecke especially, who described the particular endometrium in 1882, emphasized that it was not an endometritis but a pure hyperplasia called forth by uterine hyperemia. Cullen in this country called attention as early as 1900 to these endometrial hyperplasias and has repeatedly referred to the condition in his various publications since then. Brennecke conceived deficiencies in ovulation as explaining the uterine congestion which continued without resolution; Adler, Aschner, Lauth, Novak and Fraenkel have also recognized the ovarian etiology and noticed the lack of fresh corpora lutea. One of the views expressed has been that the hemorrhage is a menstrual one, but one unchecked, because the corpus was not there to repress it! We owe to Schroeder the analysis of the ovarian dysfunction.

The endometrium as seen after curettage may have a distinctive appearance to the naked eye. It is often abundant and fungous or polypous with distinct tiny cysts, which are distentions of hypertrophic glands, and with many places which are reddened by bleeding. Microscopically the great thickness of the structure and complexity of the glands with their high epithelium but lack of secretion may be made out. The stroma resembles that of the basalis though it may be in places close and in others loose meshed. There are small thromboses where leukocytes, necrosis and hemorrhage can be made out. Schroeder has shown that the ovaries show large follicles with a healthy and often thick granulosa (the cells of which may show mitoses), healthy ova and enlarged cells of the theca interna,—that is, we have the persistence of large ripe follicles. The only corpora lutea which may be found are at least six to seven weeks old. The follicles have also occasionally been reported as cystically degenerating (as in the type of follicular atresia which overtakes ripe follicles) and, in which cases an hypertrophied theca interna layer can be made out (R. Meyer). It is apparent that in this condition we have a rather precise example of prolonged proliferative endometrial effects of ovarian follicular ripening, i. e., the pathological accentuation of ovarian preovulation effects on the remainder of the reproductive system and a complete absence of the transformations effected normally by the corpus luteum on account of the long delay and indeed failure in ovulation. One must confess that both the non-luteinous granulosa and the theca interna may be concerned here; the latter is reported as frequently hypertrophied. Scientific interest in the

malady cannot fail to center in the apparent proof which it affords of the dependence of the so-called "secretion" changes characteristic of the pregravid endometrium upon a functioning corpus luteum. If a corpus does not exist these secretion changes do not occur. But there may be a remarkable continuance of proliferative phenomena in the endometrium as long as ripe follicles continue to live and hence exert this effect. An analogy with this disorder has been found in the delay of ovulation and prolonged life of ripe follicles which may be found in some animals. Long and I have detected this condition as a rare anomaly in the rat, and it is interesting to note that a continued vaginal epithelial proliferation and desquamation, which, as the diagram of Fig. 1 shows, is the normal pre-ovulatory or follicular effect, continues to be exhibited for a period of from two to six or even twenty days, instead of for thirty hours as is normal. The ovaries exhibit large unruptured follicles. These findings are thus seen to harmonize with our conviction of the distinction to be made in the responses of the uterus to the ovaries during the two phases of ovarian activity which occur respectively before and after the ovulatory act.

The Morphological Pathology of the Ovaries as Endocrine Organs . . . . . *James R. Goodall*

Gonococcal Infections—Tubercular Infections—Septic Infection—Infection Complicating the Acute Fevers—Morphological Changes Due to Abnormal or Arrested Development of the Ovaries—Errors Due to Arrested Development—Hemorrhages—New Growths of the Ovary—Changes in the Ovary Incident to Defective Uterine Pregnancy—Climacteric Changes.

The Morphological Pathology of the Ovaries as Endocrin Organs

JAMES R. GOODALL

MONTREAL

The morphological pathology of the ovaries has always been a difficult study. The difficulty seems to arise out of the numerous classifications of ovarian new growths. The types of pathological processes are so numerous that no one classification seems to cover all the cases. This difficulty has arisen chiefly through an improper knowledge of the development of the ovary. Authors have described invasions of the ovary by segments of the Wolffian body. Others contend that the Wolffian body is a normal constituent of the human ovary and that many pathological processes bear characters which stamp their origin from the Wolffian body. Other organs have also been described as entering into the construction of the normal ovary. Until quite recently it was almost universally thought, due chiefly to the teachings of Waldeyer, that the germinal epithelium of the ovary did not penetrate farther than the outer cortical third of the ovary. Whatever glandular structures were found within the hilus or medulla of the ovary were thought to be due to the invasion of the ovarian stroma by the tubules of the Wolffian body. The Wolffian body, or mesonephros, was consequently divided into two portions: that which invaded the ovary was called the genital portion, whereas that outside the boundaries of the ovary was called the urinary portion of the Wolffian body.

In order to acquire a proper knowledge of the pathology of the ovary it is first necessary to determine the true origin of the parenchyma of the ovary. Accordingly, a short review of the most recent work upon ovarian development will allow of an easy comprehension of the multiplicity and varied nature of the pathological processes and developmental errors.

The author has found that the human ovary contains three distinct types of tissue:

1. The connective tissue of the ovary.
2. The "interstitial cells" of the ovary.
3. The oögenetic tissues.

The first type of tissue, derived from the mesoblastic tissue of the Wolffian body, presents very little change in its pathological processes from that of similar tissue in other parts of the body, except perhaps modifications due to position and environment.

The second class of tissue is derived from the germinal epithelium covering the ovary through multiplication of the cells underlying the germinal cells. They are of a much higher order of development than those of the previous group. Their true nature was in doubt until the splendid work of Miss Lane-Claypon and Miss McIlroy placed our knowledge on a sound basis. These cells having the same origin as the true oögenetic cells, possess much of the potentiality of the oögenetic tissues. These cells have a normal function of secretion which may pass over readily into a pathological state owing to morbid conditions.

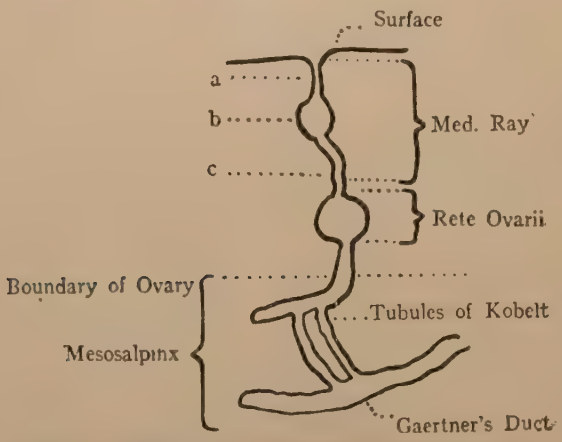

Fig. 1. Diagram of development of the ovary.

From author's work, "The Origin of Tumours of the Ovary." *Surg. Gyn. and Obst.*, vol. xxx, No. 3, March, 1920, pp. 249-263.

The third type of tissue has to do with reproduction, the development and maturing of the ovum, and the growth of pregnancy. These cells of this third group are the result of the downgrowth of the germinal epithelium and at one state of their fetal development (testicular stage) form continuous tubes or cellular columns which pursue a devious course from the cortex of the ovary to the rete ovarii and thence as tubules to form a union with the Wolffian body beyond the confines of the ovary. (Vide Fig. 1.) At a later stage of development portions of these medullary rays develop into primordial ova, whilst other portions atrophy and disappear. The retention of many of these latter portions, which normally should have disappeared, constitute the fetal rests of the adult ovary. These are found in every adult ovary, but in some in such small proportion as to make it difficult to find them; in others such fetal rests are abundant.

Arrest of development may take place at any stage of development and such ovaries retain permanently structures which are usually only a temporary development. There will be occasion to revert to this later.

The ovaries as endocrin bodies have a dual function. The secretion of the interstitial cells is more or less continuous throughout sexual life, whereas that of the generative cells is special and more or less intermittent.

Pathological processes may affect these two secretory structures separately or together. Not only is the ovary subject to the general morbid changes incident to other organs but owing to their special cellular nature the ovary has disease processes that are characteristically ovarian.

The morphologicopathological changes may be classified as due to infections, errors of development, nutritional changes, new growths, and changes secondary to pathological processes in the products of pregnancy.

Gonococcal Infection

The most common type of infection of the ovaries is that brought about by the gonococcus. In the vast majority of these cases the disease limits itself to a perioöphoritis only, in which it is questionable whether much or any of the secretory tissues suffer permanent damage. But in a percentage of cases, variously estimated from 2 to 5 per cent, low grade abscesses of the ovaries develop by means of the entry of the gonococcus into the recently ruptured Graafian follicle, there giving rise to a purulent accumulation of greater or lesser activity. Many such cavities may become infected giving rise to numerous isolated purulent foci. In such cases the secretory surface of the corpus luteum is gradually broken up and the cavity becomes lined by inflammatory tissue or, in less acute conditions, lined by a flattened, compressed fibrous capsule infiltrated more or less with leucocytes.

In still more acute pelvic gonorrheal cases the whole ovary may become enlarged, edematous, and infiltrated, and on resolution complete atrophy of all oögenetic and special secretory structures may follow.

Tubercular Infections

Tubercular infections of the ovary are seldom, if ever, primary. Two clinical types are easily differentiated. In the one there is a slow, progressive fibrosis of the ovary with enlargement of the whole organ and with few areas of caseation. At times the ovaries so affected may reach a considerable size. Giant cells may be few or many, and after the fibrotic process has gone on the oögenetic and secretory tissues undergo destruction. On the other hand in the more acute infections the whole ovary may become riddled with small and large tubercular cavities, and here again all trace of secretory function and oögenesis disappears.

Septic Infection

This most frequently follows puerperal infection in which the ovaries become involved with the other tissues of the pelvis, either by direct lym-

phatic extension or by invasion from the peritoneal cavity. In the early stages the interstitial tissues of the ovaries become much enlarged by edema and infiltration of their tissues. The Graafian follicles shed their membrana granulosa, the follicular fluid becomes turbid and the ova die. The corpora lutea become cystic and, if the condition should last a considerable period of time, and be sufficiently acute, and finally resolve, destruction of all specialized tissues may result and atrophy follow. In other cases pus formation takes place either in a recent corpus luteum or in the interstitial tissue, and the whole ovary becomes converted into a large pus sac or isolated small pus collections.

Infection Complicating the Acute Fevers

First to be noted among these is acute double oöphoritis complicating mumps. This complication is fortunately rare. The condition bears all the clinical signs of a diffuse, usually double, oöphoritis in which all the tissues are involved. The ovaries may enlarge to the size of a grape fruit and be followed by atrophy of the parenchyma and loss of function. When removed years afterwards these ovaries are small and of almost cartilaginous hardness, and show not a vestige of the normal functioning structures of the normal organ.

A similar condition may follow scarlet fever. I saw such a case some years ago complicating scarlet fever. The subject was a girl of eighteen and she never menstruated after this affection, though for four years previous she had been quite normal as to pelvic function. Upon opening the abdomen five years after for another condition, the ovaries were found atrophic, hard, and measured, roughly, 1.5 centimeters from pole to pole. Pelvic function was never re-established and she is sterile though now married many years.

This condition may also follow the other infectious fevers.

Morphological Changes Due to Abnormal or Arrested Development of the Ovaries

1. Total or partial congenital absence of the ovaries, though rarely seen, is occasionally met. From a morphological viewpoint these cases are of no interest.

2. *Hermaphroditism.*—True hermaphroditism is the existence in the one individual of both ovary and testis and is among the very rarest of anomalies. Furthermore one or both of the organs are sexually immature. Pick was able to collect only four authentic cases in the literature. Three forms are recognized:

(1) Those in whom one ovary is developed on one side and a testicle on the other.

(2) Those in whom there are ovary and testis on one side and either ovary and testis, or neither, on the other side.

(3) Those in whom there are both ovary and testis on both sides.

3. Excessive development of ovaries as endocrin organs. The gynecologist and pathologist meets with many cases in which the ovaries are abnormally large, greatly scarred, filled with small (so-called) cysts, giving rise to the small so-called cystic ovary. These conditions are frequently found in women who have borne many children. Upon careful preparation and examination of such specimens one finds that in most of these cases one has to do with ovaries that are functioning much beyond the normal. The primordial ova are literally packed in a minimum of interstitial tissue, many are in the various stages of development to maturity and many are ready to rupture. The ovarian surface is much scarred by these numerous follicles that have matured and there are corpora of all stages of development and degeneration. Every finding points to an excess of reproductive activity with its sequence of increased glandular formation. Stained with Sudan one finds fatty (probably) secretory cells in large numbers scattered throughout the ovaries.

4. Deficient development of ovaries as endocrin organs. In these the ovaries are small, rather smooth of surface, almond shaped, and with few, if any, visible Graafian follicles. On section, few immature Graafian follicles are seen and few remains of corpora lutea. Primordial ova are rare and the interstitial cells show very few signs of secretory activity. The cause of this and the former defect is probably to be found in heredity.

Errors Due to Arrested Development

It is the opinion of the author that many such cases are due to sudden changes in the blood supply of the ovary. In some cases there would seem to have been an arrest of development in the prenatal state whereby the ovary remains fixed in the state of development to which it had arrived at the time of the changed or arrested blood supply. Owing to the sudden vascular change a temporary state of development becomes permanent. In such cases one finds one or both ovaries filled with ducts or solid columns of cells of germinal epithelial origin coursing throughout the ovary, at times cut up into small segments, at other times cystic in character. Not infrequently only a segment of one or both ovaries is so affected. The interstitial tissue in such ovaries or segments of ovaries is sparse and more like adult fibrous tissue. Evidences of secretion and oögenetic activity in the ovary or portions of ovaries cannot be detected. Not infrequently the fetal rests in such ovaries take on a variety of aberrant growth.

Hemorrhages

Hemorrhages into the various tissues of the ovary are not uncommon. This condition is found most frequently associated with the acute fevers, but occasionally the condition develops independently of any known cause. In these cases of hemorrhage the condition may arise as a diffuse hemorrhage into a recent corpus luteum and extravasation into the peritoneum, or the condition may give rise to a diffuse extravasation of blood into all the tissues of the ovary, destroying all the Graafian follicles that have begun to mature by invasion of the cavities of these and destruction of the ova. It is probable that the hemorrhages give rise to only a temporary check to the normal functioning of the ovary.

New Growths of the Ovary

As stated above, the human embryo is made up of two types of tissues of similar origin, the interstitial tissues and the glandular tissue. It is doubtful whether in the adult these tissues having once been differentiated, can ever take on the other's function (interchange of function).

The tumors of the interstitial tissue are interesting from the point of view of their varied morphology. In the one tumor one may find tissues closely resembling sarcoma, perithelioma, endothelioma, and carcinoma. Among solid tumors the mixed variety is most common. The peritheliomata predominate. This protean property of the interstitial cell is traceable, I think, to its origin from the germinal epithelium, and as such it possesses potentialities which we do not find in other cells. In the lower animals these interstitial cells can, in exceptional cases, even take on the characters of oögenesis and mimic the normal process so closely indeed as to easily deceive the unwary student.

The oögenetic tissues of the ovary give rise to a very large variety of new growths, greater indeed and more varied than those of any other organ. This again, I think, is due to the great potentials of these cells which have had impressed upon them the power of reproducing the many and varied tissues that compose the human body. The structures from which these tumors arise are the ova and follicles and the fetal remnants of the germinal downgrowths.

These structures can and do give rise to growths of almost every nature and by their very nature they can give rise to very mixed growths. The cystic growths are most frequently large and may be lined with any kind of secretory surface. The contents of the cysts vary with the character of the lining cell. Cysts usually destroy all ovarian activity of a high order and the ovarian stroma becomes stretched out over the surface of

the cyst and is not recognizable as normal ovarian tissue. Papillomatous growth and malignant change are not infrequent.

Carcinoma arising from these structures varies from carcinoma in other organs by the fact that one may find glandular forms, tubular forms, cystic and solid forms of the new growth in the same mass. Carcinoma is usually bilateral. Ovarian function probably ceases early in the disease.

Adenomata of the ovaries are fairly common, usually solid, frequently of large dimensions, and not infrequently contain malignant characters, though such may not be detectable with the microscope. These probably also arise from the fetal structures of the ovary. It is quite the common new growth of the ovary in childhood, due, it is thought, to faulty development. There is usually no normal ovarian tissue to be found in such cases.

Dermoids and teratomata are of common occurrence in the ovary. Whether these are similar in origin and nature is still a disputed point. In the case of small dermoids normal ovarian function may be seen going on in the immediate vicinity of the growth, but I have never seen this occur in cases of teratomata of the ovary. The teratomata contain the three embryonic layers well developed, though perhaps not equally. In the dermoids the ectoblastic layer predominates so as to mask the other layers, though it is stated by many that careful search will always bring the three layers to light, thus placing these two types of new growth in the same class.

Connective tissue growths of the ovary are rare, as are also myomatous tumors.

Changes in the Ovary Incident to Defective Uterine Pregnancy

In cases of pregnancy in which the ovum or placenta has undergone pathological changes certain morphological changes of the ovary are frequently met.

In cases of hydatiform cystic disease of the placenta and in cases of chorioepithelioma one finds, not only all the changes incident to a normal pregnancy but it is frequently found that nearly all the Graafian follicles, whether mature or immature, become cystic and the periphery of these cysts is made up of large oval or polygonal cells in which fatty droplets, deeply staining with Sudan III, are readily seen. As a rule such a condition of excessive secretory function is merely a temporary one, subsiding with the removal of the diseased process in the uterus. Those follicles whose peripheral cells have undergone such secretory activity are usually obliterated and their ova undergo destruction. This

whole picture would seem to be but an exaggeration of the normal changes found in the ovary incident to pregnancy.

In normal pregnancy, in addition to the development of the corpus luteum of pregnancy, there develops an increase in lutein cells about most of the follicles of ova that have begun to mature. These ova, whose follicular cells become so affected, are doomed to destruction. Under certain ill-defined pathological conditions of pregnancy such physiological development of secretory activity becomes much exaggerated, even to such a degree as to involve nearly every interstitial cell in the ovary. Notably these changes are found associated with chorioepithelioma of the uterus, and hydatiform degeneration of the placenta. Sufficient study has not yet been brought to bear upon the subject to offer any adequate explanation, though we must look upon such excessive cellular change as pathological, in all likelihood the process is merely temporary.

Climacteric Changes

The changes in the ovarian tissue due to the climacterium are of a physiological nature. The changes are of the nature of sclerosis. In many women the changes become marked very early in sexual life and then become pathological. One might aptly describe it as premature ovarian senility.

Under such pathological conditions the ovary presents all the characters incident to the climacterium. The functional sclerosis of the vessels becomes very marked and the destruction and absorption of the products incident to reproduction become less and less complete until eventually the ovary becomes filled with thick-walled vessels and corpora candicantia. The interstitial cells atrophy and disappear and their place is taken by adult fibrous tissue, except in the cortical third of the ovary where the interstitial cells disappear more slowly than is the case in the medulla of the ovary.

Influence of the Ovary on the Development of the Female Generative Tract . . . . . *Emil Novak*

Introductory—Ovarian Influence on General Organism of Woman—Influence of Ovary During Fetal Life—The Influence of the Ovary During Infancy and Childhood—The Influence of the Ovary During Adult Life—The Rôle of the Ovary in Menstruation—Modern Conception of Menstruation—Which Constituent of Ovary Is Concerned with Menstruation?—Mechanism of Menstruation—Clinical Syndromes Referable to Disturbances of Ovarian Secretion—Introductory—Quantitative Disorders—Primary and Secondary Hypogenitalism—Agenitalism Due to Congenital Absence of Both Ovaries—Agenitalism Due to Castration in Early Life—Agenitalism Due to Castration in Later Life—The Menopause—Early Menopause—Cessation of Menses—Vasomotor Symptoms—Psychic Symptoms—Nervous Symptoms—Other Symptoms—Functional Amenorrhea and Oligomenorrhea Due to Hypogenitalism—Introductory—Etiologic Considerations—Varieties—Amenorrhea of Pregnancy—Lactation Amenorrhea—Amenorrhea Due to Disturbances of Other Ductless Glands—Amenorrhea Due to Mental and Psychic Factors—Amenorrhea Due to Acute and Chronic General Disease—Amenorrhea Due to Change of Climate—Hypertrichosis in Relation to the Ovary—Female Eunuchoidism—Primary Dysmenorrhea—Introductory—Importance of Hypoplasia of the Uterus—Functional Uterine Bleeding.

The Female Gonads and Their Diseases

Influence of the Ovary on the Development of the Female Generative Tract

EMIL NOVAK, M.D.

BALTIMORE

Introductory

Ovarian Influence on General Organism of Woman.—The influence of the ovary on the general organism of the woman is undoubtedly different at different ages. Puberty apparently marks the parting of the ways as far as the secondary sex characters of the two sexes are concerned. Up to that time the general physical and psychic characteristics of the girl do not differ very markedly from those of her boy playmate. The female child is likely to be of the same angular outline as the male, and the two mingle with little consciousness of the difference in sex.

When puberty occurs, however, there is a pronounced physical and psychic transformation. In the girl, the outlines of the figure become fuller and more rounded, owing to a deposit of subcutaneous fat. The breasts become more prominent and there is a growth of hair on the mons veneris, the vulva and in the axillæ. Two important physiological phenomena, menstruation and ovulation, are now inaugurated, both of them due to the awakened activity of the hitherto dormant ovary. In addition to these well recognized functions of the ovary, however, it probably exerts an important influence on the morphological development of the generative tract.

Influence of Ovary During Fetal Life.—To say that the fetal ovaries possess no function is, of course, unwarranted. There is no evidence, however, of any important influence on the general body growth of the fetus. Indeed, it has not been definitely demonstrated that the fetal ovary is essential or even important to the early development of the generative tract. In all of the reported cases of congenital absence of one ovary (Kossman, Mayer (*d*)), the uterus has been normal. Such observations, it is true, can carry but little weight, in view of the fact that the hormone from one ovary, being blood-borne, can, of course, exert its effect on the Müllerian ducts of both sides.

More valuable would be the study of cases of congenital absence of both ovaries, which anomaly, however, is exceedingly rare. Nagel states that this defect is always associated with complete absence of the internal genitalia and with other grave malformations. This assertion, however, is contradicted by Mayer, who believes that the uterus may be present in such cases, although always of rudimentary type. He attempted a direct solution of the problem by the experimental intra-uterine castration of the female fetus. The operation was performed by transabdominal opening of the maternal uterus and the castration of the fetus in utero. Unfortunately, this unique experiment was without result, owing to the occurrence of fatal infection.

Mayer's view is that the growth of the uterus in fetal life is not dependent upon the presence or activity of the ovaries, but that it follows the general laws of body growth. In passing, it may be stated that the maternal ovary is certainly not of great importance to the fetus, as shown in many cases by the birth of perfect children in mothers who have for one reason or another been surgically castrated early in pregnancy. The corpus luteum, so important in the later physiology of the ovary, can play no rôle in the early development of the generative tract, for this structure is not found before the age of puberty.

Aside from the ovary, the endocrine structures which must be considered as possibly important during the fetal phase are the pituitary, thymus, adrenal and pineal bodies. In the present state of our knowledge, it seems unprofitable to speculate as to the exact relation of these structures to the female generative tract during fetal life.

The characteristics of the internal genitalia at this period are well known. The uterus is, of course, small, measuring about 5 mm. in length in a fetus of 76 mm. (12 weeks' development), 9 mm. at about the fifth month of fetal life and 26 mm. at birth. It is simply a straight, or almost straight, tube of uniform caliber, presenting practically no differentiation into corpus and cornu. In view of the undoubted importance of the ovary in the later development of the corpus uteri, the exceedingly rudimentary condition of this portion of the uterus in fetal life bears out what has been said above as to the subordinate rôle of the ovary in fetal life.

The Influence of the Ovary During Infancy and Childhood.—These two epochs are considered together, because of the fact that, from the standpoint of the ovary, they are similar. Indeed, what has been said concerning the rôle of the ovary in the fetus applies to these two epochs as well. The genital tract remains practically stationary, so that it is often difficult to distinguish, from its size or shape, the uterus of a newborn babe from that of a girl of 8 or 9 years.

The Influence of the Ovary During Adult Life.—The onset of puberty is unquestionably due to the awakening activity of the ovaries. The old

dictum of, "Propter uterum solum mulier est quod est" has become obsolete. It was Virchow who said, "Woman is woman by reason of her generative glands. All the peculiarities of her body and mind, everything, in fact, which in the true woman we admire and revere as womanly, is dependent upon the ovary."

The various distinctive signs of sex which make themselves evident in each sex at the age of puberty—the difference in voice, in body contour, in mammary development, etc.—were designated by John Hunter as the "secondary sex characteristics." It is still a moot question as to whether these are due to the activity of the gonads, or whether they are to be looked upon as innate racial characteristics of the two sexes, irrespective of a possible gonad influence. The latter view is ably championed by Tandler and Grosz (*f*), and endorsed also in the recent comprehensive contribution of Hofstätter. Biedl, on the other hand, believes that the secondary sexual differences are dependent on the activity of the gonads. While the question is not to be looked upon as settled, it is perhaps true that the gonad theory is held by the majority of investigators.

Although the ovary, at the age of puberty, may be said to dominate the endocrine activities of the female, it must not be assumed that the other endocrine organs plan no rôle in the characteristic developmental changes of this period. That the thyroid, pituitary and suprarenal are of great importance in this connection is amply illustrated by the influence of functional abnormalities of these organs on both the primary and secondary sex charactertistics of the female. This idea is epitomized by Bell (*a*) (*c*), in his revision of Virchow's dictum, already quoted, viz.: "Propter secretiones internas totas mulier est quod est."

From a local standpoint, the most conspicuous change of puberty is the marked increase in size of the uterus, which may almost double in size within a very short period. The increase affects almost altogether the body of the uterus, which portion is apparently under the direct control of the ovary. The cervix may remain almost stationary in size. These changes are well shown by a comparison of two of my specimens, one representing the uterus of a child of 9, the other that of a child of 14. The length of the 9-year-old uterus is 35 mm., while the 14-year-old organ is 57 mm. in length. The cervices are almost equal, one measuring 22 mm., the other 27 mm. The body of the 14-year-old girl's uterus, however, is more than twice as large as that of the 9-year-old child, measuring 30 mm. as against 13 mm.

The Role of the Ovary in Menstruation

Modern Conception of Menstruation.—It has been known for more than a hundred years that the occurrence of menstruation is dependent upon the ovaries. Until comparatively recent years it was believed that the ovarian influence is exerted through the medium of the nervous system. This, indeed, was the basis of the theory of Pflüger (*a*), enunciated in 1865, and quite generally accepted for many years. According to this theory, menstruation was to be looked upon as due to a reflex pelvic

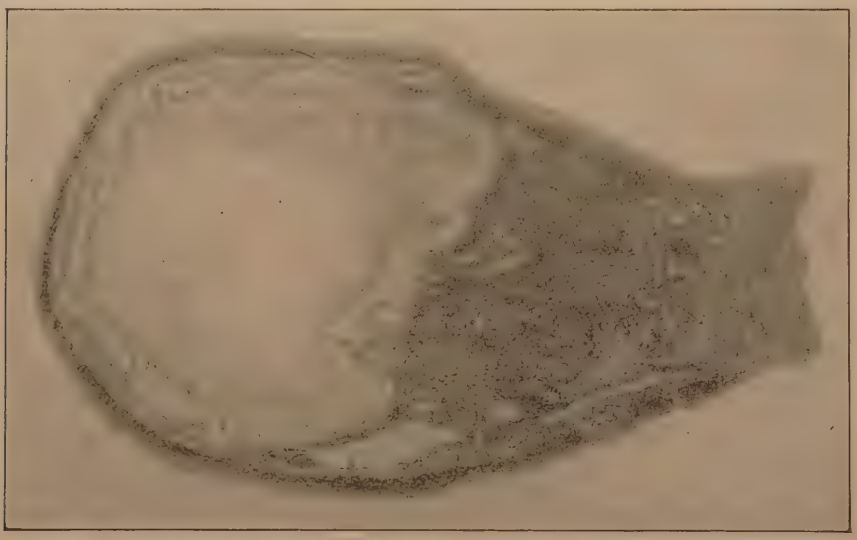

Fig. 1. A transverse section of the ovary, about three times the normal size, showing a large, mature corpus luteum.

hyperemia, evoked by afferent impulses originating in the terminations of the ovarian nerves, as a result of the pressure of the growing Graafian follicle. This theory was convincingly disproved by the work of Knauer (*c*), Marshall (*k*) and others, who showed that menstruation, or the corresponding phenomenon in the lower animals, still continues after removal of both ovaries, provided that they be transplanted into some other part of the body. In other words, the ovarian influence is blood-borne, i. e., it is of hormone nature.

Which Constituent of Ovary is Concerned with Menstruation?—As to which constituent of the ovary is responsible for the internal secretion so essential for the occurrence of menstruation, we cannot as yet speak with precision. The weight of evidence is overwhelmingly in favor of the view that it is the corpus luteum which plays this essential rôle. Some authors, like Marshall and Runciman, are inclined to the view that it is the growing Graafian follicles which are most concerned. Still

others attach much importance to the so-called interstitial cells (Zwischenzellen), although these cells in the human female are well developed only in the pregnant state. For a full discussion of this question, the reader is referred to the numerous special articles dealing with it.

Mechanism of Menstruation.—To summarize the prevailing views, it may be stated that the corpus luteum, beginning its life history at the time of ovulation, passes through a series of developmental changes which reach their acme just before the onset of the next menstrual period (Fig. 1). Hand in hand with this development of the corpus luteum there proceeds a similar hypertrophic change in the endometrium, also reaching its high point (premenstrual stage) just before the onset of the next period. The clinical phenomenon of menstruation, with its discharge of blood, is indicative of a catabolic or destructive process in the endometrium, when conception does not occur. It is a transition of the endometrium from the highest to the lowest point of its development. On the other hand, if the ovum has been impregnated, the premenstrual hypertrophy of the endometrium passes on by easy stages into the formation of the early decidua.

So much seems to be well supported by the evidence at hand. It should perhaps be emphasized that while the corpus luteum is essential for menstruation, it is not, of course, the cause of the actual menstrual hemorrhage. The rôle of the corpus luteum is to prepare the endometrium for the reception of a possible impregnated ovum. The actual menstrual discharge is synchronous with the beginning of retrogression in the corpus luteum, as Labhardt emphasizes in his recent article. The influence responsible for this has not as yet been determined, but there is reason to believe that it is associated in some way with the ovum discharged at the preceding ovulation. Perhaps it is the death of this ovum which determines the beginning of the retrogressive changes in the corpus luteum and in the endometrium.

Clinical Syndromes Referable to Disturbances of Ovarian Secretion

Introductory

Quantitative Disorders.—Our knowledge of the clinical syndromes dependent upon functional disturbances in the ovary is still very imperfect. A few facts have, however, crystallized out with a fair degree of clearness, so that we are beginning to recognize certain clinical pictures as indicative of either an excess or a deficiency of the internal secretion of the gonads. It is perhaps best to confine our discussion to these quantitative disorders—agenitalism, hypogenitalism and hypergenitalism—for the term dysgeni-

talism conveys no definite significance in the present state of our knowledge.

Primary and Secondary Hypogenitalism.—There are certain clinical syndromes which are known to be due to primary disturbance of the gonads. This group may be designated as *primary* hypogenitalism or primary hypergenitalism, as the case may be. In other cases, however, the aberration in the function of the sexual organs may be well marked, and yet it may be possible to demonstrate that the primary disease is in the pituitary, thyroid, suprarenal, or some other ductless gland. This *secondary* type of functional disorder is perhaps best illustrated in the case of the sexual hypoplastic change (hypogenitalism) associated with pituitary disease, in the case of the well-known adiposogenital dystrophy. Whether we are dealing, in such cases, with an actual secondary hypogenitalism, or whether the pituitary exerts its effect in some direct fashion on the generative tract, is problematic, but tentatively, at least, it seems best to designate cases of this type as secondary hypogenitalism.

Primary Hypogenitalism (Hypogenitalismus, hypogonadism, hypo-ovarism, hypo-oöphorism).—Several different clinical syndromes, arising in several different ways, may be associated with hypogenitalism, or deficiency of the genital, i. e., the ovarian, secretion. Complete removal of ovarian tissue is obviously productive of a condition of agenitalism, analogous to the condition brought about in the male by removal of the testes, and designated as eunuchism. The symptoms of *female eunuchism*, like those of the male form, depend a great deal upon the age at which the castration is performed.

Agenitalism Due to Congenital Absence of Both Ovaries.—The few reported cases of this anomaly are all found in the older literature, and the correctness of some of the reports is open to serious question. Nagel and Gebhard believe that this condition cannot occur except with absence of all the other genital organs and in association with other anomalies incompatible with life. Olshausen, on the other hand, believed that a rudimentary uterus or vagina can be found in such cases.

Agenitalism Due to Castration in Early Life.—Surprisingly little is available in the literature concerning the effects of complete removal of the ovaries in early life, that is, before puberty. Early castration in the male is an operation far more frequently done, and attended with definite local and general effects on the boy. The only reference in the literature to the effects of early castration in the human female appears to be the much quoted one of Roberts, a missionary, whose observations were carried out many years ago in India. According to these, the effects of such an operation are to cause a marked inhibition of the generative apparatus, as well as of the mammary glands. The secondary sex characteristics are said not to appear. As Biedl points out, however, these observations are probably of no scientific value, inasmuch

as the operation in the cases observed seems to have been, not a genuine castration, but merely a mutilation of the external organs. Tandler and Grosz quote Miklucho Macley (reference not given) as reporting a case of castration in early girlhood occurring in Queensland. The breasts were described as only slightly developed and there was little subcutaneous tissue. The buttocks were lean and there was hair upon the chin. No mention was made of any disproportion in the development of the skeleton.

The results of animal experiments, as reported by Hegar (*d*), Altertum, Pfister, Glaevecke, Bucura and others, seem to show that removal of the ovaries in early life causes a retardation of the entire genital apparatus, the uterus and tubes remaining rudimentary. It seems fair to conclude that the results of castration in the girl before puberty are probably of a similar nature.

The experimental studies of Sellheim (*b*) (1899) upon female animals are of interest in this connection, in that they demonstrated that castration in early life is productive of skeletal changes analogous to those observed in human eunuchism—the disproportionately long extremities, the retardation of epiphyseal closure, etc.

The well-known work of Tandler and Grosz (*b*) upon the results of castration as observed in the Russian religious sect known as the Skopzi led to the division of eunuchs into two principal types. In one, the individual is tall and thin, with smooth, and, in males, beardless face, the countenance being round and rather wrinkled. In the "fat" type of eunuch, there is a marked adiposity, especially in the lower abdominal region, the mammæ, the buttocks and hips.

In both types it seems to be agreed that there is a loss of sexual feeling, while it is common to observe such symptoms as loss of energy, poor memory, and various actual psychoses, in the case of neuropathic individuals (Goodell, Pfister, Glaevecke, etc.).

Agenitalism Due to Castration in Later Life.—The complete surgical removal of ovarian tissue is an operation now so frequently performed that the resulting clinical picture is well known. It does not differ in any material way from the syndrome presented by the normal menopause. The impression has been current among gynecologists that the symptoms of the artificial menopause are more severe the earlier in life the ovaries are removed. The statistics of Culbertson, however, do not bear out this idea, and I have myself been impressed with the slight degree of disturbance often following castration when this is made necessary in very young women. The personal equation appears to be the prime factor in regulating the severity of the symptoms, just as in the case of the normal menopause. The symptoms of the surgical climacteric are so similar in character to those of the natural menopause, next to be discussed, that one description will suffice for both.

Changes in the voice after castration have been described by Peasler (quoted by Tandler and Grosz) and Moure. In the two cases reported by the latter the voice became stronger and deeper. Bottermund also believes that, whereas in castrated males the voice tends to become boyish in character, the reverse is the rule in castrated women, in whom the voice tends to assume a masculine character.

The appearance of hirsutism after castration has been described by Atler (Tandler and Grosz), and also by Von Herff, in whose cases the appearance of a beard, and of hairy growth in the mammary and sternal regions, was noted.

The Menopause

The Menopause (Climacterium, climacteric, "change of life").—The normal menopause, with the train of annoying symptoms so often attendant upon it, is due to the physiological *anoöphorism* (anovarism, agenitalism, agonadism) which occurs in women at a certain age, as a result of the withdrawal of the internal secretory activity of the ovary.

The recent exhaustive statistical study of Sanes (*b*), based on the literature from thirty-two nations, places the average age of the menopause in all the cases at 47.1 years. In a general way, Webster is probably correct when he says that "in temperate countries it takes place in about fifty per cent. of women between forty-five and fifty; in twenty-five per cent., between forty and forty-five; in twelve and one-half per cent., between thirty-five and forty; and in twelve and one-half per cent., fifty and fifty-five."

Early Menopause.—Cases are not infrequently encountered in which the menopause occurs at an unusually early age. Kisch, for instance, mentions the case of a Jewess who began to menstruate at 9, married at 15, bore no children, and ceased to menstruate at 17. It is interesting to note that this patient was described as having been fat from childbirth. This, indeed, is a very common observation, as I have had occasion to note in the cases of early menopause I have myself encountered.

Whether these cases are to be looked upon as instances of primary hypogenitalism, or whether they are to be considered as secondary to disorders of other endocrine glands, especially the pituitary, it is difficult to say. From the fact that they exhibit all the characteristics of the usual hypopituitary type of amenorrhea, it is probable that they should be classified under this head, and that the amenorrhea and other symptoms referable to the sexual organs are the result of a secondary hypogonadism. Certainly this would seem to be true as regards the patients who exhibit a marked degree of obesity, and these patients constitute the overwhelming majority. In the less frequent cases, in which there is no increase of weight, it is possible that the primary disturbance is to be sought elsewhere than in the pituitary.

Symptoms of the Menopause.—The endocrine disturbance characteristic of the climacteric may in some cases exert a profound effect upon the entire organism, with the production of numerous and severe clinical manifestations. In other cases, again, the endocrine apparatus adjusts itself more smoothly and rapidly to the withdrawal of one of its cogs, so that there may be scarcely a symptom produced. While there are few women so fortunate as to be spared all symptoms, it is probable that the significance of the menopause as a disturber of the woman's health and well-being is exaggerated, especially in the minds of the laity. It is, after all, one of the physiological phases of woman's life, even though many women experience considerable annoyance in their passage through it. The principal symptoms of the menopause may be enumerated as follows:

1. Cessation of Menses.—This symptom, which gives the menopause its name, is clearly due to the cessation of the internal secretory activity of the ovary—a physiological agonadism which is preceded by a varying period of hypogonadism. The menstrual function does not usually disappear abruptly. Much more frequently the cessation of menstruation is gradual, and in some cases many months elapse before the "dodging period" of the menopause passes into a permanent amenorrhea.

While not usually looked upon as a normal phenomenon, and while it should always be regarded with suspicion, it is true that not a few patients exhibit an increase in the menstrual flow during the menopausal period, even in the demonstrable absence of anatomic diseases, such as cancer, fibroids, etc. These cases of so-called functional climacteric bleeding are probably due to a temporary hypersecretion of the ovary, as will be discussed under another heading.

2. Vasomotor Symptoms.—Next to the actual termination of menstruation, the most striking symptoms of the menopause are those referable to the vasomotor system. Most conspicuous are the *hot flushes,* which involve especially the head and neck, and the *heat flashes,* which affect often the entire body. Among other symptoms perhaps referable to the vasomotor system are sweating, vertigo, faintness, epistaxis, vicarious bleeding from various parts of the body, cold sensations in the hands and feet, etc. Certainly these vasomotor symptoms are found in some degree in about 80 per cent. of all cases.

Cause of Vasomotor Menopausal Symptoms.—As to the mechanism of the production of these symptoms, various theories have been suggested. Culbertson believes they "represent an instability of arterial tension." He states that the ovarian deficiency occurring at the menopause produces a relative oversufficiency of the pituitary and adrenals, causing thereby what he terms a "vacillating hypertension." Others (Schuster, Gluzinski, etc.) seek for an explanation of these symptoms in a hyperfunction of the adrenals, which are intimately associated with the sympathetic nervous system.

3. Psychic Symptoms.—These may assume various forms, such as *irritability* or *depression*. In extreme cases, especially where there is a hereditary taint, actual *psychopathic conditions* may supervene. In these cases, which are fortunately relatively rare, the influence of the menopause is similar to that of any other crisis affecting the patient's life.

4. Nervous Symptoms.—One of the most interesting, though relatively uncommon, symptoms which may be observed at the menopause is *tachycardia*. There is much plausibility in the view which has been suggested by Kisch (*b*) and others, that this symptom is the result of a relative hyperthyroidism produced by the withdrawal of the ovarian secretion. Other nervous symptoms, whose endocrine relations are not very clear or direct, are *numbness* and *tingling* of the extremities, *pruritus* (either general or genital), *headache* and *vertigo*.

5. Other Symptoms.—Among other symptoms occasionally noted are *gastric disturbances* (the dyspepsia uterina of Kisch), *constipation*, and *skin eruptions* of various sorts, the most frequent form being urticaria. Sexual desire and gratification are said to be diminished or lost in a large proportion of cases (Glaevecke, Pfister and Moll).

Anatomic Changes of the Menopause.—The menopause marks the beginning of senility in the woman, and the characteristic anatomic changes seen in the reproductive organs at this epoch are all indicative of retrogression. The external genitalia show atrophy and a disappearance of the fat of the labia, while the vagina becomes narrower, as a result of the same process of senile atrophy. The internal genitalia likewise become atrophic. The uterus is much diminished in size, while the endometrium becomes thin and fibrous, the glands being sparse and almost obliterated (Fig. 2). Especially striking are the changes exhibited by the ovaries, which become small and of dense, fibrous texture. The follicles disappear and corpora lutea are no longer found. The differentiation between the cortical and medullary zones of the ovary becomes very sharp (Fig. 3).

In a large proportion of cases women exhibit a tendency to a greater or less *increase in body weight* at the menopause. Glaevecke found a significant increase in body weight in 57.5 per cent. of castrated women, Alterthum (Tandler and Grosz) in 29.5 per cent. As throwing light on this frequently observed fatty deposit may be mentioned the work of Löwy and Richter (*b*), who found that castration brings about a decrease in the oxygen interchange in the tissues of as much as 20 per cent. In some cases the increase of body weight is very great, more frequently it is moderate. The fat is deposited especially in the anterior abdominal wall and about the hips and buttocks. Often the face also shows a heavy deposit of fat. Occasionally there is a loss of weight at the menopause, but this is exceptional. The breasts often become large, fat and pendulous, as a result of a fatty periglandular deposit, although the gland tissue itself exhibits atrophic changes. Rarely a secretion of milk may appear in the

breasts at the menopause, as in the case reported by Landau, and also a series recorded by Alterthum.

Diagnosis.—As a rule, the diagnosis of the menopause is simple enough, but occasionally the problem is rather difficult. It becomes necessary at times to determine whether amenorrhea occurring at the menopausal age is actually menopausal in character, or whether it is due to pregnancy. Not infrequently women who are anxious for childbirth are

Fig. 2. Senile endometrium from a patient aged 49 years.

deceived by menopausal amenorrhea and menopausal increase in the size of the abdomen into the conviction that pregnancy exists (pseudocyesis). It is often difficult to disillusion such patients, even when pelvic examination shows that the above symptoms are associated with no increase in the size of the uterus and, perhaps, an actual atrophy.

Treatment.—In many women the discomfort caused by the menopausal manifestations is so great that treatment is indicated. It need scarcely be said that the higher the standard of general health the less troublesome the symptoms are apt to be. For this reason it is important to urge such general measures as the avoidance of worry and anxiety, the securing of an abundance of sleep, the avoidance of constipation, etc. Drugs are frequently resorted to for the relief of such symptoms as ner-

vousness, insomnia, headache, etc., especially the various nerve sedatives, such as the bromids. Since this medication is along symptomatic lines, it need not be detailed here.

The only rational therapy of the vasomotor symptoms of the menopause—and it is these of which the chief complaint is usually made—is by the administration of organ extracts, especially those derived from the ovary. Indeed, there is no field in which such extracts yield more

Fig. 3. Senile changes as seen on transverse section of ovary.

satisfactory results than in this group of cases. The statement of Burnam that improvement is noted in no less than 90 per cent of cases is not, in my opinion, exaggerated.

There has been considerable discussion as to the type of extract to be used in these cases, and especially as to the relative merits of extracts made from the entire ovary and those made from the corpus luteum alone. My own feeling has been that the latter are more desirable in the treatment of symptoms revolving about the menstrual function, while the ovarian extracts are perhaps more clearly indicated in the developmental disorders associated with gonadal dysfunction. For this reason I have usually employed corpus luteum extract in the treatment of the meno-

pausal vasomotor symptoms. The results, as I have already stated, have been gratifying, if not brilliant. Others have reported results just as satisfactory from the use of ovarian extracts.

It is difficult to suggest the dosage of these preparations, owing to the lack of standardization of the products put forth by the various manufacturing pharmacists. It would scarcely be in good taste to specify them by name. Generally speaking, the corpus luteum extract is given in doses representing about five grains of the dried extract, administered three times a day, in either capsule or tablet form. Some advocate much larger doses, but I have personally rarely seen good results from the very large doses when moderate amounts of the extract have been of no avail. The corpus luteum extract is prepared also in a soluble form suitable for hypodermic administration. This has become quite popular with many gynecologists. The solution is prepared in convenient ampule form, one ampule being injected at intervals of two or three days, depending upon the severity of the symptoms.

The ovarian extracts are likewise used in either tablet or ampule form. The literature of the various manufacturing houses is easily available, giving full details of the preparation and the dosage. Recently Graves has reported encouraging results from the use of what he calls ovarian residue, an extract prepared from the ovary after separation of the corpora lutea. Tyler has also reported favorably on the results yielded by this preparation, although it is too early to decide whether it will yield results any better than the preparations already spoken of.

Occasionally other ductless gland extracts are of value in the therapy of the menopause. In the obesity which sometimes develops at this period, thyroid extract is frequently resorted to, either alone or in association with the ovarian extracts. The principles governing its use are similar to those applying to thyroid medication generally. The dosage should usually be small, owing to the fact that its administration is prolonged. Ordinarily one or two grains a day is a sufficient dose for prolonged employment. At times pituitary extracts are also used, as in the treatment of the functional uterine hemorrhage of the menopause. This subject will be discussed under a separate heading.

Functional Amenorrhea and Oligomenorrhea Due to Hypogenitalism

Introductory

Etiologic Considerations.—In a much larger proportion of cases than is commonly believed, amenorrhea (absence of menstruation) or oligomenorrhea (scanty menstruation) are the results of endocrine disorders, rather than of local disease in the pelvis. This is in contrast with the

etiology of excessive menstruation, which is to be sought in local pelvic disease far more frequently than in constitutional causes, endocrine or otherwise. In a small proportion of cases, amenorrhea is the result of congenital or acquired disease or anomalies of the pelvic organs, such as absence of the uterus or of the ovaries. In the latter case, the absence of menstruation is clearly due to a total agenitalism or anoöphorism. Much more interesting, however, are the cases of amenorrhea which are so frequently observed in the entire absence of any gross anatomic disease of the pelvic organs. Most of these are undoubtedly due to hypogenitalism, although, as already emphasized, it is not always easy to determine whether this deficiency of ovarian function is primary or secondary in nature.

One other distinction seems worthy of mention. In some cases, the extreme type being represented by complete removal of the ovaries, the amenorrhea is due to a genuine anoöphorism, or hypo-oöphorism, as the case may be, i.e., the function of the entire ovary, with its probably several hormones, is in abeyance. In this group the amenorrhea is practically always associated with constitutional or developmental changes of one form or another. This type is well illustrated by the well-known adiposogenital dystrophy, to which fuller reference will be made later.

In a second group, on the other hand, the amenorrhea appears to be due to a deficiency of only the menstruation-producing hormone of the ovary—that of the corpus luteum. Menstruation is absent, but no other noteworthy changes are seen. This is well illustrated in the amenorrhea of lactation (see below). In cases of this type the hormone of the corpus luteum alone is either antagonized or inhibited, so that a condition of what may perhaps be called *hypo-luteinism* or *a-luteinism* is produced.

The principal causes of amenorrhea as they relate to the endocrine system may be grouped as follows:

Physiological Amenorrhea.—At puberty and at the menopause it is common to observe a so-called "dodging period," characterized by intervals of amenorrhea of varying lengths. These are obviously to be explained by the gradual inauguration of ovarian secretion at the first-named epoch, and by its gradual cessation at the other extreme of menstrual life.

Amenorrhea of Pregnancy.—Amenorrhea is the normal status during pregnancy. There are some who would explain this as due to a cessation of ovulation during pregnancy. There can be no doubt, however, that the inhibiting influence of the living embryo is a factor of great importance in the causation of the amenorrhea in either intra- or extrauterine pregnancy. In the latter, for example, the appearance of uterine hemorrhage is usually indicative of the death of the embryo, as, indeed,

it is also in intra-uterine gestation. This fact was elaborated upon in a recent paper by the writer.

Lactation Amenorrhea.—Amenorrhea is the rule during lactation, or, at any rate, during its earlier part. Ehrenfest (*b*) has well emphasized that in a very large proportion of cases—81.3 per cent—menstruation reasserts itself sooner or later, even though nursing of the child be continued. The amenorrhea of lactation is undoubtedly due to the inhibiting or antagonistic influence of the lactating-breast hormone upon the function of the corpus luteum. Ovulation occurs and corpora lutea are undoubtedly formed throughout lactation, even though menstruation be absent. The best proof of this is the frequent occurrence of pregnancy in nursing women. This group presents perhaps the best illustration we have of what we have called hypo-luteinism.

Amenorrhea Due to Disturbances of Other Ductless Glands.—*Thyroid.*—Amenorrhea may be observed with either hyperthyroidism or hypothyroidism. There has been considerable discussion as to this point, but the weight of evidence seems to support the view of Hertoghe that hyperthyroidism is far more likely to be associated with scantiness or absence of the menstrual function than is hypothyroidism.

Pituitary.—A frequent and exceedingly important cause of amenorrhea is hypopituitarism. Every gynecologist and every practitioner of medicine encounters numerous cases in which amenorrhea is associated with obesity. The older textbooks were wont to explain the amenorrhea as due to the adiposity, or vice versa. As a result of the researches of Fröhlich, Paulesco, Cushing and others, we now know that this is not the case, but that both the obesity and the amenorrhea are due to the same underlying cause—a deficient function of the hypophysis. While in Fröhlich's first case of adiposogenital dystrophy the autopsy showed a pituitary tumor to be present, it is important to remember that amenorrhea is frequently due to hypopituitarism, even though no tumor is present. In these cases the pituitary disturbance does not seem to inhibit ovulation, but rather to counteract the endocrine function of the corpus luteum. The author has observed several cases in which pregnancy has occurred in the course of hypopituitary amenorrhea, in one case of three years' duration.

Suprarenals.—The functional differentiation of the cortex and medulla of the suprarenal bodies has been fully discussed elsewhere. It is sufficient here to repeat again that the interrenal system, of which the suprarenal cortex forms part, is closely related, from a functional standpoint, to the gonads. The syndrome of hypersecretion of the cortex, usually associated with suprarenal tumors, and combined with evidences of premature and excessive sexual development, is better known than the opposite condition.

There are cases reported, however, in which suprarenal atrophy or

hypoplasia have been associated with a secondary hypogonadism, as manifested by retarded sexual development. In the case of Wiesel, for example, a girl of eighteen presented an infantile condition of the genitalia, the mammæ were practically absent, the nipples very rudimentary, there were no axillary hairs and practically none on the mons veneris. Autopsy demonstrated a striking hypoplasia of the adrenals. Similar cases have been recorded by Karakascheff, Gelford and Zander.

Amenorrhea Due to Mental and Psychic Factors.—Amenorrhea is occasionally the result of such psychic causes as sudden fright. It may also be due to an intense longing for pregnancy (pseudocyesis), or to a dread of its occurrence, as in the case of girls fearing themselves illegitimately pregnant. Finally, it is observed in a large proportion of insane women. The exceedingly prevalent form of amenorrhea observed in the continental countries, especially Germany, during the great war (Kriegsamenorrhöe), was the result of under-nutrition, combined with the profound psychic influences secondary to war conditions. It is useless to speculate as to the mechanism of the amenorrhea in these cases, although it would appear difficult to explain it except on endocrinologic lines.

Amenorrhea Due to Acute and Chronic General Diseases.—It is common to observe amenorrhea with the acute infectious diseases, and also with the chronic debilitating affections. Especially striking is its frequency as an early symptom of tuberculosis and of anemia. Here also we are undoubtedly dealing with a hypogonadism secondary in some way to the systemic condition.

Amenorrhea Due to Change of Climate.—This is a not infrequent and exceedingly interesting cause of amenorrhea, often of many months' duration. It is difficult to see how a change of climate or environment could produce amenorrhea except through some influence, as yet unknown, on the endocrine apparatus.

Treatment.—Drug medication is rarely of value in the treatment of amenorrhea, except in that type due to chlorosis and the other forms of anemia. In these cases the administration of such hematinics as iron and arsenic brings about an indirect emmenagogue effect, with restoration of the function. The value of such general measures as fresh air and proper food is obvious in all cases.

The organotherapy of functional amenorrhea varies somewhat with the type of the disorder. In some cases it is of course not indicated, as in the amenorrhea associated with such debilitating diseases as tuberculosis, diabetes, etc. The same statement applies to the forms of physiological amenorrhea which were enumerated above. In the primary form of amenorrhea, associated with delayed puberty, ovarian extracts are frequently resorted to. Here the entire ovarian substance would seem to be preferable to the corpus luteum extract. It is often combined with extract of the pituitary, either of the entire gland or of the anterior lobe. In a

few cases, delayed puberty may be an indication of hypothyroidism, in which case thyroid medication is of course indicated.

The functional amenorrhea of later life is treated along similar lines. The cases associated with hypopituitarism make up perhaps the largest group. The organotherapy of these is considered at length elsewhere. Thyroid, the various pituitary extracts (entire gland, anterior lobe and posterior lobe), and ovarian extracts, have all been employed by various workers. Polyglandular medication has achieved a wide vogue in the treatment of such cases.

In the cases which seem to be due chiefly or entirely to hypogenitalism, the rational treatment consists in the administration of ovarian extracts over a long period of time. Some prefer extracts of the entire ovary, some extracts of the corpus luteum alone. The results cannot be said to be striking under either form of medication. It is probable that in these cases the hypogenitalism is practically always secondary, and that better results are obtainable by the administration of pituitary or thyroid extracts, either alone or in combination with the ovarian substances.

Fig. 4. Facial hypertrichosis, associated with dermoid cyst of ovary (McAuliff).

Hypertrichosis in Relation to the Ovary.—From time to time cases have been recorded in which hypertrichosis, or abnormal hairy growth in various regions, has been attributed to perversions of ovarian function. A striking case was recently reported by McAuliff (Fig. 4). His patient was a woman of 63, who presented an excessive growth of grayish hair on the upper lip and chin and a moderate amount on the cheeks. The woman suffered with a pelvic tumor, which at operation proved to be a dermoid cyst of the left ovary. Hypertrichosis has also been described in association with such anomalies as uterus duplex (Hegar), uterus unicornis (Freund) and uterus infantilis (Hildebrand, quoted by Hegar). It has also been attributed to such acquired conditions as cystic ovaries (Röten, quoted by Scheuer), and various tumors (Alberti).

It is exceedingly doubtful, however, whether this symptom should be

explained as due to ovarian secretory disorders. It is far more frequently and more characteristically observed in association with disease of the suprarenal bodies and occasionally of the pineal body. It it perhaps best to consider it as a manifestation of pluriglandular disturbance.

Female Eunuchoidism.—*Rarity of the Condition.*—As compared with the corresponding condition in males, female eunuchoidism is exceedingly rare. Indeed, only a few authentic cases are to be found in the literature. The following abstract is given by Falta of the case reported by Josefson and Sundquist:

"Thirty-four-year-old woman, who had kept on growing from the fifteenth year on (the growth had been especially active up to the twenty-fourth year); she was 183.6 cm. tall (upper length 118 cm.), she had never menstruated and had felt only slight inclination for men; the mammæ were small, flat, without palpable glandular substances, the nipples very small; she had rather a mannish appearance, but a feminine voice. The form of the pelvis was rather womanly. The epiphyseal junctures were closed, the sella turcica not enlarged. Examination of the genitalia showed very small labia minora, a hypertrophic clitoris, the vestibule was rather narrow, the internal genitalia were not palpable. No introitus vaginæ or hymen."

Another case which Falta looks upon as an instance of probably genuine eunuchoidism is that reported by Neurath. The patient was described as an eleven-year-old tall-grown girl of typical "eunuchoid" obesity.

Characteristics.—As in the case of male eunuchoids, the three most striking features of eunuchoidism, as manifested in women, are (1) the characteristic skeletal proportions; (2) the typical fat distribution; (3) a greater or less degree of genital hypoplasia.

The Skeletal Characteristics.—Practically all eunuchoids are tall. At any rate, they are never below the average height. This is of some importance as a point of differentiation from such conditions as adiposo-genital dystrophy. There is a pronounced retardation of epiphyseal closure. Especially striking is the disproportionate length of the extremities as compared with the trunk. This feature is always more marked in the lower extremities.

The Distribution of Fat.—The characteristic eunuchoid distribution of fat is marked by heavy deposits of adipose tissue especially in the region of the lower abdomen, the mons veneris, the buttocks, and the outer sides of the thighs. Frequently there is a deep furrow between the accumulations in and above the mons. In many cases there is a marked adiposity of the mammary glands.

Genital Hypoplasia.—While eunuchoidism is the result of a hypo-ovarism, it is not usually possible to demonstrate clinically an actual hypoplasia of the ovaries themselves. The uterus and vagina, however, are always hypoplastic, and may be absent altogether, as in the case

of Josefson and Sundquist, to which reference has already been made. Sexual feeling is always rudimentary or absent, and sterility is the invariable rule.

Differential Diagnosis.—Especially difficult is the differentiation between eunuchoidism and infantilism. Indeed, the confusion of the two terms in the literature is very perplexing. Some authors, notably Wolf and Peritz, are inclined to look upon eunuchoidism as only a form of infantilism, a view which Falta, with what seem to be good reasons, has vigorously opposed. Infantilism is characterized by a preservation of the child type of body proportion—the long trunk as compared with the relatively short extremities, the low position of the navel, the relatively large head, etc. All these are in contrast to the findings observed in cases of genuine eunuchoidism. Furthermore, the mentality of the eunuchoid, while subnormal, is hardly of the childish, retarded type seen in cases of infantilism. Finally, in the latter condition, we not only do not observe the characteristic adiposity seen in the eunuchoid, but, as a matter of fact, the patients are apt to be quite slender and gracile.

The other condition which may easily be confused with eunuchoidism is adiposogenital dystrophy. In both conditions we find a hypoplasia of the genital organs, in the one case primary in the gonads, in the other secondary to hypopituitarism. In both, however, there is adiposity, of somewhat similar distribution, although the hypopituitary patient often shows rather characteristic accumulations about the shoulder region ("shoulder pads"). As already stated, however, the true eunuchoid is practically always tall, with abnormally long extremities—characteristics lacking in the hypopituitary syndrome. In the latter, finally, there are apt to be, in the case of pituitary tumor, pressure symptoms, such as headache.

Scope of the Term "Eunuchoidism."—Many authors have extended the application of the term eunuchoidism to include cases of pituitary, adrenal, thyroid or other ductless gland disorders characterized by atrophy and loss of function of the genital glands. Climenko and Strauss, for example, have recently reported several cases of "eunuchoidism," which they ascribe to pituitary disease. Falta, on the other hand, limits the scope of the term to those cases in which the sexual glands themselves are primarily at fault, and in which, in addition to the sexual underdevelopment, there are present such characteristic symptoms as the typical disproportion between the trunk and the limbs. This would seem to be the proper viewpoint.

Late eunuchoidism occurring in adults as a result of severe disease of the genital glands has been frequently described in men, but no case has been reported in the female.

Treatment of Female Eunuchoidism.—Little need be said concerning the treatment of this rare condition, especially since the results are not

striking. The indication would seem to be clear for the administration of ovarian extracts, those derived from the entire ovary being preferable in this condition to those derived from the corpus luteum alone.

Precocious Puberty

Definition.—*Average Age.*—The average age of puberty in girls in the United States is a little less than 14 years (13.9 years). There is, of course, a wide margin of individual variation. When puberty, as manifested by the first menstruation, occurs before the age of 9, it is spoken of as precocious. In the great majority of cases, the precocious menstruation is associated with other manifestations of an awakening of the sexual apparatus—a rounding of the figure, the growth of hair on the mons veneris and in the axillæ, development of the breasts, etc. These cases are, therefore, properly spoken of as cases of precocious puberty.

Causes.—It seems certain that hypergenitalism is the causative factor in precocious puberty. It may be either primary or secondary. An example of the primary, or ovarian, etiology is furnished by the case of Brohl, in which premature puberty, with menstruation, was observed in a girl of seven. The removal of a large cystic ovary was followed by the disappearance of the menstrual function. Similar cases have been recorded by Lucas, Guthrie and Emery, Hofacker and others. More frequent are the cases of hypergenitalism secondary to disease elsewhere in the endocrine chain, especially in the suprarenal and pineal bodies. Bulloch and Sequeira have described a series of cases of suprarenal tumors, chiefly hypernephromata, associated with sexual precocity. Newman, in 1901, reported as many as 22 cases in which tumors of the pineal gland were found with precocious maturity. In many cases of sexual precocity, however, there is no indication of the existence of a tumor.

Diagnosis.—This presents no difficulty as a rule, although the recognition of the cause may not be easy. Many cases have been reported as instances of precocious menstruation which are in reality cases of the simple non-menstrual hemorrhage of the new-born. The latter condition is characterized by a single hemorrhage, usually slight, occurring commonly on the fifth or sixth day after delivery. Genuine precocious menstruation, on the other hand, occurs usually at a later age, and is characterized by the regular periodicity of its recurrence.

Treatment.—Although the condition is of endocrine origin, no satisfactory form of organotherapy can be advised, in the present state of our knowledge. It should be emphasized that sexually precocious children are usually subnormal mentally, and hence they should be guarded against the dangers of sexual violation. Many instances of pregnancy have been reported in cases of this type. The youngest patient, so far as I have

been able to find, was only six years old when pregnancy occurred. This case was reported by Mandeslo (quoted by Lenz).

Primary Dysmenorrhea

Introductory.—*Endocrinologic Relationship.*—At first sight there would seem to be little connection between primary dysmenorrhea and the endocrine system, and yet I believe that an important relation of this sort does exist. By primary dysmenorrhea we mean that form of menstrual pain which occurs in the entire absence of discoverable disease in the pelvis. It is observed with great frequency in young nulliparous women, either single or married, and is the cause of a great deal of suffering. The factors which have been considered instrumental in the causation of this form of dysmenorrhea are as follows: (1) Mechanical obstruction of the cervical canal; (2) the neurotic factor; (3) hypoplasia of the uterus.

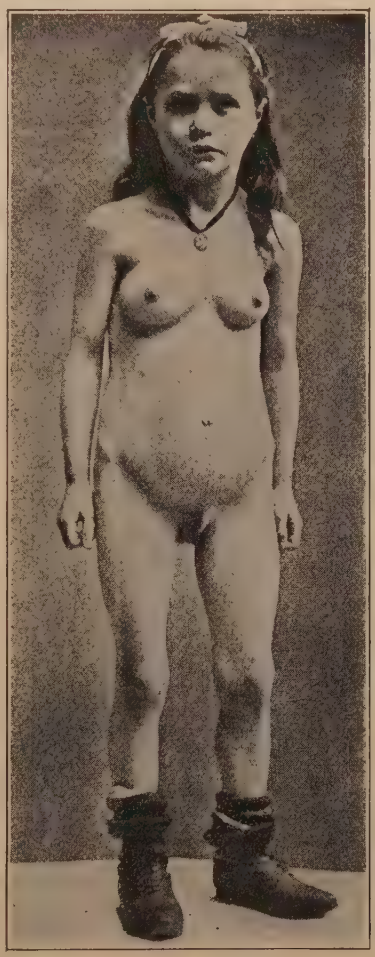

Fig. 5. Precocious development in a girl of six.

Importance of Hypoplasia of the Uterus. — *Etiology.* — There is little doubt that by far the most important of these factors is a defective development of the uterus. It is extremely common to find a greater or less degree of genital hypoplasia in women whose development otherwise is quite normal. This cause of uterine hypoplasia may be classified under three heads, according to the degree of hypoplasia: a. The fetal type (Fig. 6), in which the arrested development occurs at a very early stage, so that the uterus is of the fetal type. The special characteristics of the latter are its small size and the fact that it is made up almost entirely of cervix, the corpus uteri being exceedingly rudimentary. b. The infantile type (Fig. 7), in which the uterus resembles that normally found in infants and young children. Here again the cervix predominates over the corpus, although the latter is not as rudimentary as in the fetal type. The uterus as a whole is larger and there is often an associated ante-

flexion, most commonly of the cervico-corporeal variety. c. The subpubescent type (Fig. 8), in which the hypoplasia is relatively slight. Here, also, there is not infrequently an associated anteflexion. For a fuller discussion of these varieties of uterine hypoplasia and of their clinical significance, I would refer to a previous paper which I have published on the subject.

Cause of Uterine Hypoplasia.—The pertinence of the question of uterine hypoplasia to the present discussion depends on two factors: First, that an extremely frequent symptom of uterine hypoplasia, though not by any means a constant one, is primary or spasmodic dysmenorrhea. Secondly, that the underlying cause of the various grades of uterine hypoplasia is undoubtedly of endocrine nature. In searching for a cause for the hypoplasia, we at once make contact with the endocrine apparatus in the body. Which of the endocrine glands is responsible for the defective development of the uterus noted in these cases? In the first place, does the ovary exert any important influence on the development of the uterus before the age of puberty, that is, during the fetal, infantile and prepubescent periods of life? Certainly no such influence can be assigned to the corpora lutea, for the latter do not appear before the age of puberty. The possibility suggests itself that some other element of the ovary may possess this function, but the evidence is not convincing. As already stated elsewhere, Mayer believes that the growth of the uterus in very early life follows the general law of body growth and that it is not especially influenced by the ovaries.

There is much reason to believe that the earlier growth of the uterus is under the influence of other endocrine glands, especially, perhaps, the hypophysis. This seems especially probable in view of the undeniable rôle played by the pituitary in the production of sexual hypoplasia. For this there is abundant evidence, both experimental and clinical. It is as yet impossible to offer an exact explanation of the mechanism involved in these cases, but there seems to be little doubt that they are associated with hypogenitalism, probably of the secondary type.

Treatment.—For the treatment of primary dysmenorrhea the reader is referred to the various textbooks on gynecology. From the endocrinological standpoint, our interest in these cases is based chiefly on the possibility of relieving the dysmenorrhea by bringing about a better development of the uterus. For this purpose pituitary extract, especially in the form of the anterior lobe, would appear to be indicated, although I am frank to say that I have not been impressed with the results of this form of medication in the cases in which I have employed it. The same statement applies to the results of the administration of the various ovarian extracts, either alone or, as is more frequently done, in combination with the pituitary substance.

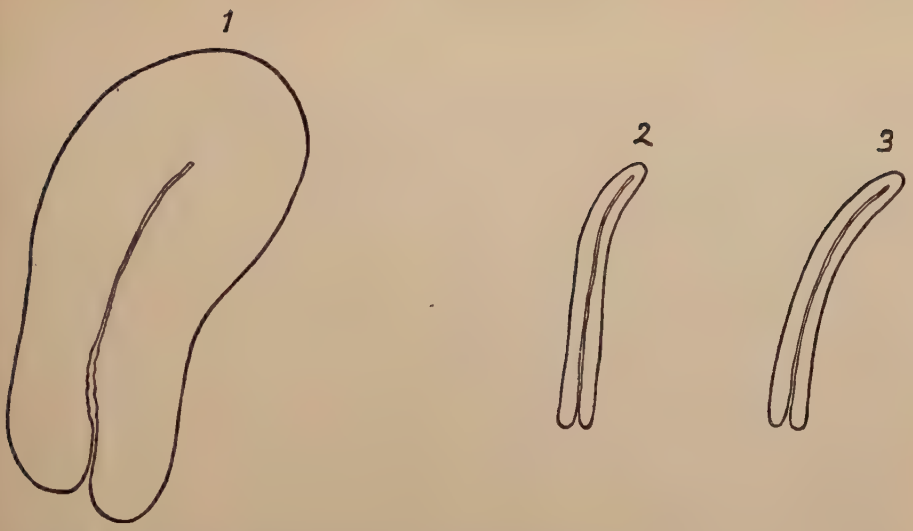

Fig. 6. The fetal type of uterine hypoplasia (Uterus Rudimentarius or Fetalis), 2 and 3, as compared with the normally developed uterus, 1.

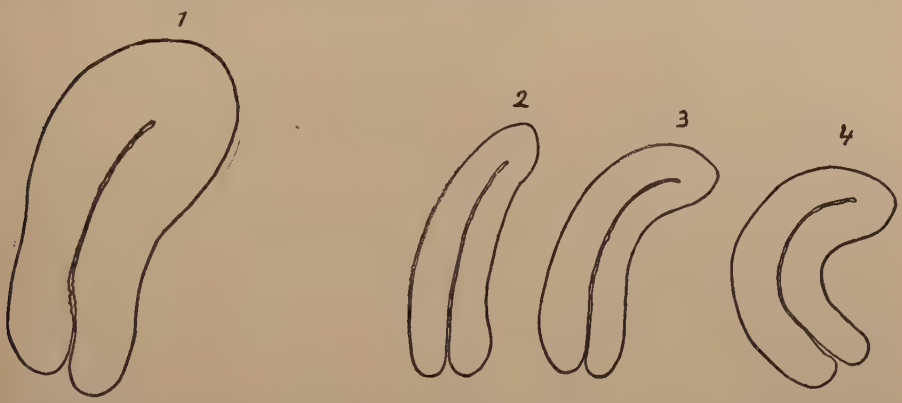

Fig. 7. Types of infantile uteri (2, 3 and 4), in comparison with the normal uterus (1).

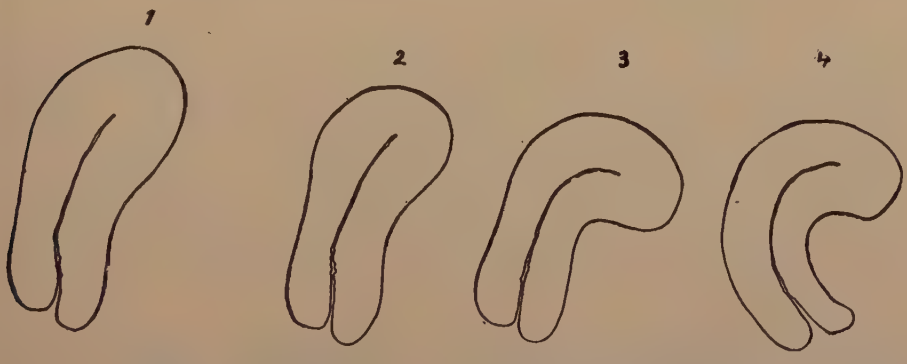

Fig. 8. Types of subpubescent uteri, showing only slight differences in size from normal uteri (1).

Functional Uterine Bleeding

"Idiopathic" or Essential Uterine Hemorrhage.—Another gynecological complaint, the endocrine origin of which permits of very little doubt, is the so-called functional, "idiopathic," or essential uterine hemorrhage. This symptom is of very frequent occurrence, especially at the two extremes of menstrual life, puberty and the menopause. It may, however, occur at any age. In these cases the most careful examination may show perfectly normal pelvic organs, and yet bleeding may be persistent and perhaps very profuse. Most commonly it takes the form of menorrhagia rather than metrorrhagia. Cases of this type usually come to curettage sooner or later, and indeed, in the case of climacteric hemorrhage, the indication for this procedure is urgent, owing to the importance of excluding carcinoma. In the non-malignant climacteric cases and in those of puberty the pathological report on the curettings has usually been some such designation as "Normal endometrium, hypertrophic glandular endometritis, chronic endometritis," etc. It has seemed difficult to incriminate the endometrium as the cause of bleeding of this type. Equally unsatisfactory have been the efforts to explain this form of bleeding by such factors as arteriosclerosis of the uterus, the "insufficientia uteri" of Theilhaber, etc.

The point which I should like to emphasize is that the endometrium in a very large proportion of these cases—I am not prepared to put it in percentage figures—conforms to the type described by Cullen (*b*) as hyperplasia of the endometrium. The histological picture presented by this condition is extremely characteristic. As the term indicates, there is a genuine hyperplasia of the uterine mucosa, with an increase of both the epithelial and stromal elements. The histological characteristics of this condition are fully discussed in a recent paper by the author.

Secondary Nature of Endometrial Change.—An endometrium of this type is never observed except in association with the symptom of uterine bleeding. The reverse is, of course, not true, for uterine hemorrhage may be due to many anatomic causes. Most frequently the endometrium is perfectly normal. It is of interest, however, to note that with certain pelvic lesions, especially myoma and adenomyoma, the endometrium may exhibit the condition of hyperplasia, as above described. There is some evidence to believe that both myoma and adenomyoma are due to some as yet unknown aberration of ovarian function and, as we shall see, there is little doubt that the same factor is responsible for hyperplasia of the endometrium.

The finding in a case of uterine bleeding of such a definite structural alteration as hyperplasia of the endometrium would seem at once to take such a case out of the category of functional hemorrhage.

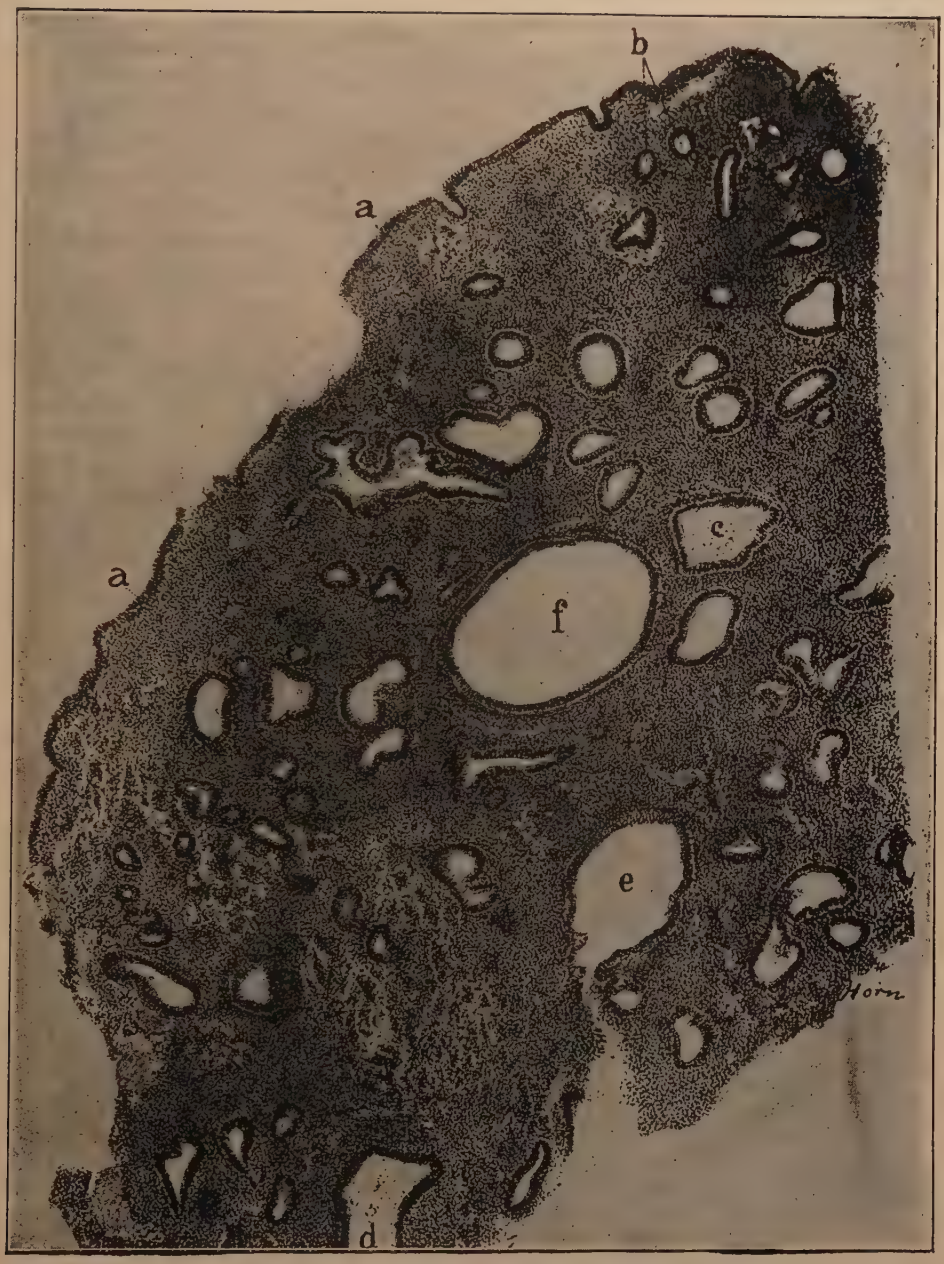

Fig. 9. Hyperplasia of the endometrium.

There is abundant evidence, however, that this characteristic change in the endometrium does not represent a primary lesion, but that it is purely secondary to a disturbed function of the ovary. Under normal conditions the endometrium is certainly subordinate to the influence of the ovary. The ever-changing histological appearance of the uterine mucosa at different phases of the menstrual cycle is undoubtedly called forth by corresponding cyclical changes occurring in the ovary, and especially in the corpus luteum. So that there is nothing revolutionary in the idea that the characteristic picture of hyperplasia may be associated with some definite endocrine disturbance of the ovary. The reasons for considering hyperplasia of the endometrium, with its accompanying "functional uterine bleeding," as manifestations of ovarian hypersecretion, are set forth in a recent paper by the author. I shall not review this evidence here, but it is so impressive that no intelligent gynecologist can afford to overlook the importance of the pathological physiology of the ovary in the consideration of possible causes of uterine bleeding.

Treatment of Functional Uterine Hemorrhage.—Among the most interesting, and also the most perplexing, problems encountered in gynecological practice is the treatment of these cases of so-called functional uterine bleeding. This type, as already explained, includes the numerous cases of functional climacteric bleeding and the less frequent cases of menorrhagia of puberty. In the majority of such cases, especially if severe, curettage is indicated, chiefly for diagnostic purposes. In the case of menopausal hemorrhage, the indication for curettage is urgent, on account of the importance of excluding cancer. Drugs are of little or no avail in checking this form of uterine hemorrhage.

From the standpoint of organotherapy, the principal difficulty is presented by the fact that we as yet know little of the endocrinopathy responsible for this form of menstrual disorder. As a matter of fact, it seems quite probable that the nature of the internal secretory disturbance varies in different cases. It is not surprising, therefore, that the results of organotherapeutic measures, semi-empiric as they must be, have been far from satisfactory. The organ extracts which deserve consideration in this connection are those of the thyroid, ovary and pituitary.

In the case of the functional hemorrhage of puberty, thyroid extract has, in my own hands, yielded the most encouraging results. To illustrate, in a recent case of persistent and profuse bleeding in a girl of fourteen, curettage seemed indicated, especially for diagnostic purposes. Microscopic examination of the curettings showed typical hyperplasia of the endometrium. The bleeding, however, did not cease. The patient was then given doses of thyroid extract of two grains a day, with almost immediate cessation of the bleeding. It is only fair to add, however, that similar medication in other cases has appeared to be of no benefit,

indicating, as has already been emphasized, that the endocrine disorder is not always of the same character.

In the more frequent cases of functional climacteric hemorrhage I have rarely seen any benefit from thyroid medication, and not infrequently the bleeding has seemed to be exaggerated. Somewhat better results have followed the administration of ovarian extracts, especially of the corpus luteum preparations. This is in keeping with recent histological investigations, which indicate that corpora lutea are commonly absent in cases of hyperplasia of the endometrium associated with uterine bleeding. In other words, even though we are perhaps dealing in these cases with a form of ovarian hypersecretion, it is not the corpus luteum which is overactive. Some other element in the ovary is concerned with the hyperfunction, the corpus luteum being deficient. My most encouraging results have been obtained from the exhibition of corpus luteum extracts, either alone or in combination with small doses of thyroid. The corpus luteum is usually given in doses representing five or ten grains of the dried extract three times a day. Or it may be administered subcutaneously in the form of the soluble extract, which is now prepared commercially in convenient ampule form (1 c.c.). One ampule is injected usually every second or third day, depending on the severity of the hemorrhages. By such measures the condition may in some cases be improved, so that the patient can be tided over the period of endocrine instability which predisposes to the development of this symptom.

As to the use of pituitary extracts, little of a definite nature can be stated. The use of posterior lobe extracts has been lauded by some. As I have stated above, however, any good results obtainable from these are probably due to the well-known effects of these preparations in stimulating contraction of the uterine musculature. The other effects of these substances are of such potency, however, as to contraindicate their continued administration for a prolonged period. So far as I know, anterior lobe extracts have achieved no important place in the treatment of these troublesome cases, and, indeed, there would seem to be no especial rationale for their employment.

It is unfortunate that we cannot be more explicit in suggestions as to the organotherapy of this important type of hemorrhage, and that our efforts to attack it along what seem to be rational lines have not met with a greater measure of success, but I believe that what has been said represents the worth-while in our present knowledge of the subject.

SECTION VII

The Mammary Glands in Their Relationships

Physiology, Physiological Chemistry and Experimental Pathology . . . . . *Frederick S. Hammett*

Introduction—The Mammary Gland as a Sex Characteristic—Growth and Development of the Mammary Glands—Control of Development—Hormone Factors in Mammary Activity—The Ovary and Mammary Activity—Menstrual Growth Impulse—Milk Secretion and the Ovary—The Corpus Luteum and Mammary Activity—The Interstitial Gland of the Ovary and Mammary Activity—Uterine Hormones and Mammary Activity—The Mammary Hyperplasia of Pregnancy—The Placental Hormone and the Mammæ—The Fetus and Mammary Activity—The Fetus and Mammary Growth during Pregnancy—The Fetal Membranes and Mammary Growth and Secretion—The Testicle and Mammary Activity—Mammary Gland Extracts as Galactagogues—The Hypophysis as a Stimulant to Lactation—The Thymus as a Galactagogue—The Pineal Body and Lactation—Endocrine Glands without Galactagogic Action—The Mamma as an Endocrine Gland—Conclusion.

The Mammary Glands in Their Endocrin Relationships

Physiology, Physiological Chemistry and Experimental Pathology

FREDERICK. S. HAMMETT

PHILADELPHIA

Introduction

The Mammary Gland as a Sex Characteristic.—The growth and development of the mammary glands, for the assumption of the secretory function and production of milk, is one of the distinguishing secondary sexual characteristics of the female. According to Pelikan the breasts are considered among certain primitive peoples, especially the Russian Skopts, to be the factors responsible for other sex manifestations. This idea Virchow has modified in the aphorism that "Woman is woman because of her generative glands." Pflüger, Hegar, and Klebs strongly objected to this conception that the somatic and psychic sexual characteristics are dependent upon the generative glands, while Tandler and Grosz are of the opinion that "what are called secondary sex characteristics are in reality only characteristics of the species, that is to say, properties peculiar to a species or an order of vertebrates and having no primary relation with the organs of generation. Thus, the mammary glands are the outcome of an agglomeration of sweat glands, which later became the engine of a different function and was included within the sphere of influence of the organs of reproduction" (Biedl).

Such an hypothesis, though appealing from a phylogenetic point of view, is somewhat weakened by the results of the investigations concerning the functions and effects of the internal secretions of the generative glands on the mammæ, these studies having shown an apparently close and intimate interrelationship existing from the earliest periods between these tissues and variations in mammary activities.

The physiology of the mamma is not only of importance with respect to the proper development of the individual, but also from the object of the attainment of a proper functioning to the production of an adequate milk secretion for the nourishment of the young; which obviously depends upon the completeness of the preliminary growth.

Growth and Development of the Mammary Glands.—*Stages of Development.*—The growth and development of the mammary glands does

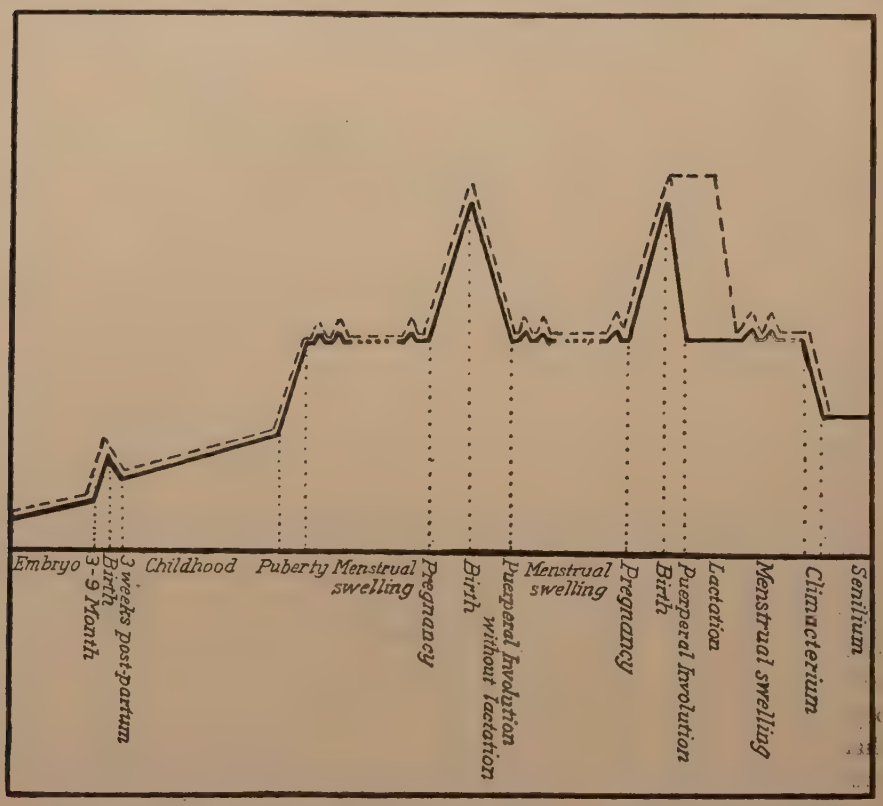

Fig. 1. Diagram of the course of development of the mammary glands and the uterus, after Halban.

not follow a continuous, smooth curve, but has in its course several sharp deviations from linear uniformity as is shown in the accompanying diagram from Halban (*c*) (1905).

The intra-uterine growth is regular and continuous until between the eighth and ninth months, when there occurs a relatively marked enlargement as the result of the first growth impulse. After birth, a slight regression is followed by growth, in conformity with the general increase in mass of the body, until at puberty the *second or pubertal growth impulse* causes the very visible development to the mature gland, ready to receive

the stimulus for its specific preparation for the taking on of the secretory function. In many individuals there is to be noted between these two phases the regular occurrence of a swelling of the mamma at the menstrual periods, which enlargment has been considered as due to the reception and response to the *third or menstrual growth impulse.* With the onset of pregnancy, there takes place the fourth type of growth and development, due to the *fourth growth impulse,* the changes occurring at this time being the final steps in the preparation of the gland for its function of milk secretion. Repetition of the changes induced by the third and fourth growth impulses occurs as circumstances direct, until the regressive stages accompanying and following the climacterium set in, and the glands, having accomplished their function, become inactive and sterile in common with the other generative organs.

It is thus possible to classify the growth changes of the mamma into four distinct groups, each of which is dependent upon the reception of and response to a definite stimulus. The development of the mammary glands, however, is merely the preparation of this tissue for taking on its particular function, the elaboration and secretion of milk, and this act of secretion is also apparently dependent upon the reception of and response to a definite stimulus.

Control of Development.—Attention was first directed to nerve impulses as the source of the stimuli bringing about these very evident changes. Goltz observed that even after the lumbar portion of the spinal cord had been removed from a bitch, the animal, on becoming pregnant, obtained a normal hypertrophy of the mammary glands and was able to suckle the young after parturition. Probably the most conclusive results were obtained by Ribbert. This investigator removed a mamma of a guinea pig from its customary location and transplanted it to the region of the ear. The animal was then allowed to become pregnant. During pregnancy the transplanted gland became enlarged, and parturition was followed by lactation. This was confirmed by Pfister. These and similar observations by Mironow, Kehrer, and others yield positive evidence that the growth of the mammary glands, at least during pregnancy and the attainment of their secretory function after delivery, is independent of the direct effect of nerve stimulation, and it will be later shown that the growth impulses at other times is likewise largely dependent upon factors other than nerve impulses.

The question whether or not mechanical stimulation of the breast, by sucking, with accompanying mechanical acceleration of the local circulation, is sufficient of itself to induce secretion, was investigated by Cliquet and Lacassagne (quoted by Halban (*c*), 1905), and by Hildebrandt. The results were negative. Freund was inclined to believe that the initiation of actual secretion was correlated with the time of greatest involution of the uterus, and that at this contraction there was squeezed

from the uterine vessels a large amount of blood into the general systemic circulation which played an important rôle in the onset of lactation. Such an hypothesis is opposed by the observation that fairly normal milk secretion frequently occurs, when the uterus is removed before the commencement of lactatory activity. Schein proposed the conception that milk secretion is brought about by the increased blood supply to the mammæ, since by the emptying of the uterus this organ has need of much less blood than during pregnancy, thus allowing of its utilization by the upper half of the body and particularly the mammæ. There is, however, no positive proof for this hypothesis and certain facts oppose its probability. For instance, when abortion occurs, even during the early stages of pregnancy, and at a time when the blood supply to the gravid uterus is not much greater than normal, secretion of milk is frequent; moreover, removal of immense ovarian and uterine tumors is not followed by any increased activity of the mammary glands, insofar as secretion is concerned, although such procedure must materially alter the distribution of the blood in the body; since neither nerve impulses nor augmented circulation account for lactation it seems probable that a qualitative change in the blood constituents in the nature of hormone stimulation is the underlying factor concerned.

Inasmuch as the factors concerned in the pubertal, menstrual and pregnancy growth impulse are rather definitely established, as well as the source of the stimulus to lactation, whereas the first or embryonic impulse is more or less a matter of conjecture, this latter phenomenon will be briefly discussed and the later stages taken up under the discussion of the relations of the secretions of the individual endocrin glands to the different periods of mammary activity.

Halban (1905), noting the occurrence of hypertrophy of the fetal mamma during the eighth and ninth months of intra-uterine life, attributed it to the stimulating influence of a placental hormone derived particularly from the trophoblast and chorionic epithelium. This opinion was based on the hypothesis that the mammary hyperplasia of pregnancy is due to a placental secretion. The hypothesis lacks exact confirmation, and is, indeed, improbable.

Hormone Factors in Mammary Activity

The Ovary and Mammary Activity.—*Pubertal Growth Impulse.*—That the normal development of the mammæ at puberty is dependent upon an ovarian function is demonstrated by the experiments of Knauer (*a*)(*b*)(*c*)(1896-1900), who found that if ovarian transplantation was followed by atrophy, the mammary development did not occur. Halban (*a*)(*b*)

(1900, 1904) added to this observation the fact that the castration of young animals prevented the onset of the pubertal mammary development, but that when the ovaries that had been removed were successfully implanted in some other portion of the organism, normal mammary growth resulted. These investigations having been confirmed by Alterthum, and supported by the work of Foges (*a*) (*b*) (*c*) (*d*) (1901-1908), and Hegar, were approved on theoretical grounds by Fellner, and no doubt, at present, exists that the ovaries play a major part in the growth of the mammary glands at puberty.

Menstrual Growth Impulse.—Knauer having demonstrated that ovarian castration inhibits the onset and duration of menstruation, Halban (1905) extended the observation to the mammary changes during menstruation, and came to the conclusion that the stimulus for the third growth impulse likewise arises from an ovarian secretion, in which opinion Lane-Claypon and Starling concur.

Pregnancy Growth Impulse.—The source of the stimulus for the mammary hyperplasia of pregnancy has occasioned much controversy. Although Basch favored the idea that the ovary constitutes the main factor involved in this, as in the other periods of growth, Halban (1905) having noted clinically that normal mammary growth occurs during pregnancy, even after bilateral ovariectomy, strongly opposed the hypothesis. The investigations of Biedl, Mainzer, Cramer and Lane-Claypon and Starling support Halban's contention, while the experiments of Lane-Claypon and Starling indicate quite another source for the stimulus. Such evidence justifies the belief that the ovary takes a minor part, if any, in the mammary growth of pregnancy.

Milk Secretion and the Ovary.—The report of Lajoux, that an increased milk secretion was obtained from cows after castration, together with the observations of Halban and others that the mammary glands go on to full secretory activity after the ovaries have been removed during pregnancy, fail to support the conclusions of Temesvary and Bächer, who claim to have obtained an increased secretion of milk after the injection of ovarian extracts. Moreover, Fellner (*b*), Lane-Claypon and Starling, and MacKenzie were unable to confirm these results, although MacKenzie, using ovarian tissue, minus corpus luteum, did obtain some galactagogue activity.

These facts and further decisive experiments, later to be described, show that the ovary is not the galactagogic agent par excellence.

The Corpus Luteum and Mammary Activity

To Prenant can be given the credit for first having called attention to the probability that the corpus luteum is a ductless gland. Interest

having thus been directed to this portion of the ovary, Fraenkel (*a*) in 1903, and later, Ferroni claimed that the mammary hyperplasia of pregnancy is attributable to the activities of the corpus luteum. On the basis of the clinical evidence already presented, and further extended considerations of Halban (*a*) (1900), this opinion could hardly be substantiated. Although Ancel and Bouin found that the destruction of the corpora lutea in pregnant rabbits arrested mammary development, and the experiments of O'Donoghue (*a*)(*b*)(*c*) indicated that this tissue is important in mammary hyperplasia, yet the carefully worked out investigations of Lane-Claypon and Starling (which have been fully confirmed by Foà and by Biedl and Königstein) leave scarcely a doubt that the corpus luteum is not the main factor in the growth of the mammary glands at pregnancy. As regards milk secretion, the evidence presented by Schafer and MacKenzie, by Ott and Scott (*b*), by MacKenzie, seems to demonstrate some galactagogic power of the corpus luteum, which, however, was not shown either in the experiments of Lane-Claypon and Starling or Fellner. Hence, the part played by the corpus luteum in the various growth periods of the mammary glands and the development of their secretory function is at the present time a matter for further investigation.

The Interstitial Gland of the Ovary and Mammary Activity

The functions of the epithelioid cells in the interstitial tissue of the ovary were considered as being local and trophic until Regaud and Policard (1901) expressed the opinion that a secretory function could be attributed to them. Bouin (1902) supported this idea on the basis of the work of his pupil Limon, who had shown the derivation of this cell complex from the theca interna folliculi. These findings and conclusions were confirmed by Cohn (*a*)(*b*) (1903, 1909) and extended by Lane-Claypon (1905). Fraenkel (*b*), however, has denied any physiological function to this tissue in human adult females. In a study of the histology of this tissue during pregnancy, Wallart and Seitz found the structures to be analogous to those in other animals. Nevertheless, Seitz would not admit that they possess an internal secretory function. Since, however, the morphological changes taking place in this cell complex show a marked development of activity before puberty and menstruation, as well as during pregnancy, which changes are accompanied by changes in mammary activity, it is not beside the mark at least to consider the possibility that the interstitial gland of the ovary has an influence upon the various and periodic changes in the mammæ.

Uterine Hormones and Mammary Activity

The Mammary Hyperplasia of Pregnancy.—The possibility that the uterus, among other tissues, is concerned in the mammary growth during pregnancy has been brought into question. Although Fellner obtained an indeterminate effect as the result of injecting extracts of pregnant uteri, neither he nor Lane-Claypon and Starling were able to demonstrate that uterine extracts stimulate mammary growth, and the probability that the uterus *per se* exerts an influence during this period is minute.

Milk Secretion and the Uterus.—Clinical evidence is ample to show that postpartum hysterectomy is not necessarily followed by cessation of lactation. Halban, Foges and Lambret have presented cases demonstrating that milk secretion may continue even though the uterus be absent. Since MacKenzie obtained a decided galactagogic effect by the injection of saline extracts of the involuting uterus, it is not improbable that the tissue at this stage does give off metabolic by-products that are stimulating to mammary secretion. This, however, does not necessarily signify that a normal function of the uterus is the production of a hormone excitatory to lactation.

The Placental Hormone and the Mammae

In the chapter concerned with the Placenta as an Endocrin Gland there will be found a discussion of the hypothesis built up around the ideas of the effect of placental secretion on mammary growth during pregnancy, and their secretory activity.

The Fetus and Mammary Activity

With the onset of conception commences the growth of the mammary glands preparatory to their taking on of the function of lactation, though it is not until the delivery of the uterine contents that this function normally is assumed. It is but natural that investigators have looked to the fetus as a possible source of the stimuli bringing about both the growth and subsequent lactation.

The Fetus and Mammary Growth during Pregnancy.—Although Halban (1905) on clinical grounds, and Frank and Unger on the basis of experimental results, consider that the fetus is not concerned in the mammary hyperplasia of pregnancy, the investigations of Lane-Claypon and Starling, which have been amply confirmed by Foà and by Biedl and Königstein, show unmistakably that injections of fetal extracts will produce a growth of mammary tissue analogous to that occurring during pregnancy. These results, by a process of eliminative experimentation,

lead to the conclusion that the stimulus to mammary growth during pregnancy is derived mainly from the fetus.

The Fetus and Milk Secretion.—The clinical observations of Kehrer, Cravin, Hofmann, de Sinèty (*a*) and others that milk secretion starts up after the emptying of the uterus, either prematurely or by abortion, combined with the observations of Hippocrates, Sinclair, Gessner, Deschamps, Keller, Busch, and others, that milk secretion may often occur when the fetus lies dead in the uterus, afford sufficient evidence to substantiate the belief that the fertilized egg produces a substance acting as a stimulus to milk secretion. The fact that the onset of a new pregnancy stops lactation, as discussed by Munk and Kleinwächter, is too well known to need further comment, and its significance in this connection is obvious.

It is a fact, moreover, that Lane-Claypon and Starling were able to induce secretion of milk in multiparous rabbits by the injection of fetal extracts. They succinctly explain that their experiments could be considered as producing a brief pregnancy followed by parturition, which naturally should be followed by the production of milk in the structures prepared for it.

The direct experimentation of MacKenzie is supported by the results of Lane-Claypon and Starling and Biedl and Königstein and shows almost conclusively that fetal extracts do exert an inhibitory action on lactation. In 1904 Hildebrandt proposed the theory that the uterine contents act as a stimulus to mammary growth, but as an inhibitor to the mammary autolytic changes which were supposed to be the essential precursors of secretion. This idea he extended to the conception that, on the removal of the uterine contents at birth, the inhibitory substance was likewise removed and the initiation of the secretory process effected. This theory coincides with the conditions as at present generally understood and elaborated in detail by Biedl.

The Fetal Membranes and Mammary Growth and Secretion

Fellner has reported that the injection of extracts of the fetal membranes has a slight stimulating effect on the mammary hyperplasia but none on milk secretion. Close inspection of his results, however, shows them to be too indeterminate to be conclusive, and the question of the effect of this group of tissues on mammary activity is still open.

The Testicle and Mammary Activity

The results of the extensive implantation experiments carried on by Halban (1905) led him to believe that the gonad tissue of either sex could

in part act as a stimulus to the pubertal mammary growth, since he found that ovarian castration followed by testicular implants did not inhibit the development of the mammæ at puberty. Opposed to this conception is the fact that the injection of testicular extracts by Fellner gave indecisive results as regards the growth and secretory activities of the mammæ, and MacKenzie obtained negative results as regards milk secretion in similar types of experiments. These investigations open up wide fields for study and speculation, being as they are so intimately connected with fundamental biological principles.

Mammary Gland Extracts as Galactágogues

In the search for substances acting as stimuli to lactation, many and varied tissue extracts have been employed, some of which have been found to have a marked excitatory action on mammary secretory function. As a result of the injection of a saline extract of mammary tissue into cats, MacKenzie frequently, but not always, obtained augmented milk secretion. In view of this fact it would be interesting to determine whether or not the presence or absence of the stimulating substance is in any way dependent upon the degree of development or relative activity of the gland from which the extract is made.

In this connection it should further be mentioned that Wilms has obtained an abundant secretion of milk in a mother whose lactation was scanty, by the administration of several successive hypodermatic injections of 3-15 minims of her own milk. This observation raises the question as to whether or not the stimulating substance is the same as that found by MacKenzie in extracts of mammary gland tissue.

The Hypophysis as a Stimulant to Lactation

The credit for first putting on record the fact that extracts of the posterior lobe of the hypophysis, when injected hypodermatically into animals, produce an increased rate of milk secretion belongs to Ott and Scott (*a*); these investigators worked with goats. Schafer and MacKenzie later demonstrated that not only *pars posterior,* but also the *pars intermedia* extracts act as stimulants to lactation. It is to be regretted that we do not yet know whether or not one of the normal functions of this gland is that of initiating and assisting in the regulation of the flow of milk, or whether this galactagogic action is accidental rather than purposeful. The fact that extracts derived from the fish stimulate milk flow may be not without significance in this regard.[1]

[1] It should be added that results obtained in Carlson's laboratory and elsewhere show that the augmentation of milk flow is due merely to action of the extract on the muscular tissue of the gland. No actual increase in milk production has been demonstrated.—R. G. H.

The Thymus as a Galactagogue

Histological evidence seems to show that the period of activity of the thymus in normal individuals hardly coincides with the time of life when lactation occurs. Yet Fellner observed a degree of hyperplasia in the mammary glands as the result of the injection of extracts of thymus; Ott and Scott (*b*) further showed that thymus extracts have some galactagogic effect, although MacKenzie has failed to confirm this. These observations raise a question as to whether the supposedly involuted thymus takes on renewed or new activity during pregnancy and lactation, or whether various endocrin glands extracts have the adventitious property of stimulating lactation, no specific function being involved.

The Pineal Body and Lactation

Both Ott and Scott and MacKenzie were able to obtain an increased secretion of milk as the result of the injection of extracts of the pineal body into animals. These experiments are significant, in that they demonstrate a possible physiological function of this tissue, which has for so long been an object of speculation as to its probable field of activity, but here again we can raise the question as to whether or not the galactagogic substance is adventitiously or functionally purposeful.

Endocrin Glands without Galactagogic Action

The extended investigations of Schafer and MacKenzie, and MacKenzie working alone, have demonstrated that among the endocrin products, secretin, as well as thyroid and suprarenal extracts, does not induce increased lactation when administered hypodermatically. Nevertheless, confirmation is lacking, and more intensive experimentation might well bring out significant results.

The Mamma as an Endocrin Gland

It was but natural that in the search for tissues presenting the characteristics of endocrin glands attention should have been directed towards the mammary gland, since not only its histological structure, but also its type of functioning would indicate the possibility of the elaboration of an internal secretion.

The mammæ have long been known to have an influence upon the other female generative organs, particularly the uterus, and this relationship has been attributed by Pfister and by Temesvary and Bächer to nerve

impulses transmitted to the uterus upon stimulation of the mammæ in various fashions.

In the line of clinical evidence, supporting the idea of a mammary influence upon the uterus, may be cited the cases of Paterson, in which a stimulation of the breasts resulted in relief from amenorrhea; then Soetcrick, Mollath and others have reported uterine contractions in pregnant women following electrical stimulation of the breasts, while Busch found that stimulation of the mammæ resulted in erection of the clitoris and secretion from the ducts of Bartholin. Although the phenomena are probably of simple reflex origin, it is within the range of possibility that the mammary stimulation releases a hormone from the mammary gland in a manner analogous to which stimulation of the splanchnics causes a liberation of epinephrin from the suprarenals. Such an hypothesis could be sustained or disproven by observing the effects of stimulation of the mammæ when all the nerves to either this tissue or the uterus, or both, are cut.

Further observations tending to demonstrate such an influence have been made by Müller and by Hermann and Stolper, who found that puerperal involution occurs sooner when the breasts are sucked than when not. In addition, the fact that continued lactation leads to hyperinvolution, as demonstrated by Frommel, Grüner, Vineburg (*a*)(*b*), Engström, and others, adds still more evidence of an underlying relationship between uterus and mamma; whether or not this is neural, hormonal, or accomplished through some other intermediary is a matter for further investigation.

The only directly available evidence that the mammary gland produces an internal secretion is the work of MacKenzie, already discussed. His results indicate that extracts of this tissue do contain substances stimulatory to lactation, an indirect support for which conclusion is found in the work of Wilms. Admitting such to be the case, we may consider that we have here either a new type of endocrin gland, a type that is self-stimulatory or autokinetic, or else that it is a property of certain types of glandular tissues, such as the pineal, the thymus, the hypophysis, and possibly others, to produce as a normal by-product of their metabolism, or to contain in and of themselves as an innate constituent of their protoplasm, a substance which has a galactagogic activity, and that the production of this stimulant is adventitious and not specific.

Conclusion

The one outstanding feature that is apparent in a consideration of mammary activity—and by activity is meant the growth, development, and assumption of function of milk production—is that the mamma more

than any other single tissue so far studied is continuously dependent upon the reception of hormonal stimulation for its successful functioning. During its entire history, from early growth and development through the periods of the taking on of its specific function of lactation, and even to the postclimacteric atrophy, it receives and responds to hormonal stimuli, and if they are lacking its activity is curtailed.

Such biological relationship between pre- and postnatal nutrition, depending as it does upon the adequate and proper functioning of the generative glands, hardly seems to uphold the idea that the mammary glands have no primary relationship with the organs of generation. Influenced and directed as they are by the internal secretions from the generative glands, there must exist a deeper and more fundamental relationship to these than that of mere adventitiousness or species characteristics.

SECTION VIII

The Placenta as an Endocrine Organ . . . . . .
. . . . . ***Frederick S. Hammett***

Early Views as to Placental Functions—More Recent Views as to Placental Functions—The Placenta as a Factor in Milk Secretion—The Placenta as a Factor in Postpartum Qualitative Changes in the Milk—The Placenta as a Factor in Uterine Changes of Pregnancy—The Placenta as a Factor in Eclampsia—The Placenta as a Factor in Growth—Conclusions.

The Placenta as an Endocrin Organ

FREDERICK S. HAMMETT

PHILADELPHIA

Early Views as to Placental Functions.—The functions of the placenta have been a subject of recorded interest since Aristotle apportioned to this organ the property of conveying blood to the fetus. Galen supplemented and extended this conception, proposing the theory that the pure blood (venous) from the uterine vessels was mixed with *Pneuma* (arterial) in the placenta and then served the fetal needs; the vegetative functions, however, such as nourishment and growth, were relegated to the liver. These views were retained until the 16th Century, when the anatomical studies of Fallopio, and later Arantius, threw much light on the relationships involved, the latter coming to the conclusion that the placenta is the tissue wherein the processes of formation and purification of blood take place preparatory to its utilization by the fetus. Further contributions by Spigelius were followed by the masterly work of Harvey, who classified the placenta as a digestive organ in which "succum alibem a matre provenientem nutriendo fœtui porro concoquit." With the expansion of the idea of a specific individuality in function for each tissue, initiated by Cartesius, the filtration theory of placental function was launched, to be later added to and supported by Haller through the applications of the then but slightly known principles of physical chemistry. This investigator characterized the placenta as being a great organ of filtration, and the custodian of the material being passed on from mother to fetus. The further development into what to-day remains fundamentally our concept of placental function with respect to fetal nutrition, has been admirably summarized and discussed in a monograph by Hofbauer (*a*), into which it is unnecessary to go. This brief historical résumé is sufficient to demonstrate that the placenta has long been an object of serious study.

The classification of the placenta as a secretory gland was probably first made by Johannes Müller, who called attention to the possibility of its possessing other functions than those of intermediary metabolism between mother and fetus.

More Recent Views as to Placental Functions.—*The Placenta as a Factor in Mammary Hyperplasia.*—The obvious changes occurring in the development of the mammary glands during pregnancy led to a series of

investigations in an effort to determine the contributing factors to this phenomenon. Although nerve impulses were at first considered as the main source of stimuli for mammary hyperplasia, the experiments of de Sinèty, Goltz, Röhrig, Rein, Mironow, Ribbert, Pfister, Kehrer, and others, demonstrated that this hypothesis was untenable since interference with the nerve supply to the breasts produced no marked hindrance in development.

Clinical and experimental observations having indicated that castration inhibits the pubertal mammary development, Halban and Knauer investigated the problem and found that when castration is followed by ovarian implantation an apparently normal mammary development occurs. From this they concluded that the pubertal impulse to mammary growth in normal females is dependent upon material secreted by the ovary. This idea was supported by the work of Fraenkel (*a*), Bouin and Ancel, and later by O'Donoghue (*a*)(*b*)(*c*), and others. It was but natural that the idea of an ovarian stimulus to mammary hyperplasia during pregnancy should be evolved. But Halban (*c*) (1905), reasoning from the clinical evidence that puerperal involution does not follow bilateral ovariectomy during pregnancy, opposed this view, and considered that "only the recently fertilized ovum can be the cause for the initiation of the changes in the maternal organism." The problem thus being narrowed down to two possible sources, Halban, by a process of reasoning, eliminated the fetus as an influence, and evolved the hypothesis that the placenta during pregnancy takes over the stimulating functions of the ovaries, the latter having but little, if any, influence on mammary hyperplasia during this period. This conclusion was apparently confirmed by Niklas and Fellner, both of whom obtained changes in mammary tissue as the result of injections of placental extracts. Nevertheless, later experiments by Mandl and Kreidl, Lane-Claypon and Starling, Foà, Basch, Biedl and Königstein, Frank and Unger, and Biedl, gave either negative or at most slightly positive results. Moreover, Foà and Basch showed that fetal extracts were effective in producing mammary hyperplasia and, taking this in conjunction with the fact that Hammett (*c*) failed to find any increased mammary development as the result of feeding desiccated placenta post partum to lactating women, when compared with the course of development in women not receiving the placental material, the evidence at hand can scarcely be considered valid for assigning to the placenta alone the function of producing a stimulus to mammary hyperplasia.

The development of the mamma is the preparation of this tissue for assuming the function of milk secretion, and the question of the origin of the source and stimulus to the production of milk has involved the possibility that the placenta plays a significant part. From early times it has been recognized that there exists a relationship between milk secretion and the functioning of the genital organs. Hippocrates noted that with the cessa-

tion of menstruation in virgins there may occur a secretion of milk. This phenomenon was also reported by Avicenna and Schacher. It is an interesting commentary upon the times that the occurrence of such a happening served to cast doubt upon the virginity of the individual reacting thus peculiarly. Aristotle assigned to milk a source analogous to the menstrual flow. The observations of Puech and Gauthier on vicarious mammary menstruation, and of Schlicter on the relationship of menstruation and lactation, all served to draw into intimate contact the functions of milk secretion and gonad activities.

The Placenta as a Factor in Milk Secretion.—*As an Initial Stimulant to Secretion.*—Obviously the most general striking evidence of a causative relationship is presented by the initiation of milk secretion in the mother after the birth of the infant. Here again attempts were made by Goltz, Mironow, Ribbert, Pfister, and others, to trace the source of stimulus to nerve impulses but without success. Clinical evidence, presented by Halban, eliminated the uterus as a causative factor, while Hildebrandt and others demonstrated that the act of sucking is inadequate for continued secretory functioning. The possibility that the change in circulatory arrangements following parturition might be a factor was summarily disposed of by Halban, for whom the act of birth alone was insufficient. Bouchacourt tentatively placed the increased milk secretion as a result of a ferment formation by the placenta, while Letulle and Nattan-Larrier, on a basis of histological studies, attributed the stimulation to the presence of a secretion demonstrable as droplets in the placental syncytium. Ercolani, Creighton, Letulle, and Pinoy considered that degenerative changes in the placenta released substances causing the assumption of the function of milk secretion by the mammary gland. Hildebrandt, correlating these various hypotheses, broached the idea that the entire uterine contents were concerned in the regulation of milk secretion, and that during pregnancy there is given off from the growing ovum an influence on the milk-producing glands in the sense of a stimulus to growth (but inhibitory to milk secretion). On the birth of the fetus, this inhibitory influence is removed, and the secretory function of the glands is taken up with increasing facility. The principle of this hypothesis was accepted by Niklas, but he tended to limit the source to the placenta, since "by the action of Ei-material [1] (placenta and fetus) it is just as possible to obtain a passing milk secretion and accompanying mammary gland hyperplasia with virgin, as with pregnant animals." Physiologically there is apparently, at birth, a flooding of the maternal blood with the stimulant that, after a certain period of incubation, initiates the activity of the mammary glands. Although Keiffer (*a*)(*b*) claimed that the placenta produces a substance regulating milk secretion and Aschner and Grigoriu, Lederer and Pribram, Basch, and others, obtained a

[1] Products of the fertilized egg.

secretion of milk as the result of the administration of placental preparations of one sort or another, thus apparently confirming Niklas, yet Kehrer, Munk and Kleinwachter opposed, and with logic, the idea of a placental influence on the basis of the fact that lactation is inhibited during pregnancy. The inhibitory influence of the placenta was conceded by Halban, Fellner, and Fieux, supported by the experiments of MacKenzie, and Gaines, and the investigations of Biedl and Königstein, Lane-Claypon and Starling, Foà and Frank and Unger presented sufficient evidence to effectually disprove the idea that the placenta has any marked stimulating effect on mammary function. As a bit of confirmatory evidence, it may also be noted that neither McNeile nor Hammett was able to observe any quantitative effect on milk secretion when desiccated placenta was fed to lactating women.

The Placenta as a Factor in Postpartum Qualitative Changes in the Milk.—Hammett and McNeile studied the effect of the ingestion of desiccated placenta on the qualitative changes occurring in the milk secreted, with the aim of determining whether or not the placenta has an influence upon the variations that take place in the chemical composition during the first few days of lactation. Eight normally lactating women ingested ten grains of desiccated placenta in capsules three times a day, beginning at delivery. The variations in the protein, fat, and lactose per cent occurring were compared with the variations in these constituents in the milk obtained from eight women not being given the placental material. Only subjects who had had normal deliveries were studied, and throughout the period of investigation the diet was the same for all. During the first eleven days after parturition, some differences in the constituents mentioned, in the experimental as compared with normal subjects obtained. Quantitatively the plane of production for lactose and protein was raised, while that for fat was slightly decreased, although the general trend of postpartum alterations in secretion remained the same in both groups. The number of subjects for this investigation was admittedly small but the results, so far as they go, show a tendency for the quality of the milk to be slightly changed as a result of placental administration.

The Placenta as a Factor in Uterine Changes of Pregnancy.—The changes taking place in the uterine substance, following the implantation of the ovum, are of such a character as to draw attention to the question of the stimulus causing the alterations. Fellner, on histological examination following the injection of placental extracts, observed an increase in uterine glandular tissue accompanied by hypertrophy. The opinion of Halban, Letulle and Nattan-Larrier and Bouchacourt that the nature of the stimulus to this hypertrophy is chemical and the source, in part at least, placental, seems to be justified.

The Placenta as a Factor in Eclampsia.—An interesting and complete historical résumé of what was known of eclampsia up to 1901 is given

by Knapp. From this account it is evident that eclampsia was well recognized clinically at the time of Aristotle. Many and varied have been the guesses advanced since that time as to the origin of the disease. That any endocrin factor is involved is improbable. The evidence by which this improbability is inferred follows.

Schmorl (*a*)(*b*) was the first to discover placental detritus in the emboli found in blood vessels of eclamptics and to attribute the eclampsia to placental interference. This hypothesis, however, resting as it did on a purely mechanical basis, was eventually demonstrated to be untenable. Even previous to Schmorl's discovery, it was becoming more and more evident that eclampsia partakes more of the nature of an intoxication than anything else. With the finding by Delore of a microörganism in the blood and tissues of some eclamptics and the apparent confirmation of the observation by Blanc, the idea of a bacterial septicemia being the cause was but natural; but from the work of Prutz and the discovery by Hofmeister that the supposedly specific organism was none other than *proteus vulgaris,* the specific causative effect of bacteria was rendered improbable. Bouchard and Rivière defined eclampsia as an anto-intoxication, while Ludwig and Savor ascribed the toxic influence to the intermediary metabolic products. The source of these intermediary products was attributed to the fetus by Van der Hoeven and Fehling, although Hitschmann claimed to be able to disprove the findings. Albeck and Lohse reported that the injection of amniotic fluid obtained from eclamptics into normal animals produced in them all the symptoms of eclampsia. This has, however, yet to be confirmed.

The trend of opinion and evidence now wandered away from the simpler metabolic by-products into the realm of the more complex substances when Kollmann and others apparently found more globulin in the blood of women in normal pregnancies than in that of eclamptics. Sjili and Dienst evolved the "fibrin theory," based in part on the frequent presence of thromboses in eclampsia, and in part on the work of Nasse. This theory was also based partly on ideas of intoxication from fetal by-products, inasmuch as Dienst considered that in eclampsia there is a regressive protein metamorphosis in the fetus which cannot of its chemotaxic ability cause a real increase in leukocytes in the maternal blood with consequent increase in fibrin precursors. That the placenta might be the seat of the changes causing the intoxication was brought out by Czempin, who held that through malfunctioning of this organ, either as a perversion or as a diminution of functional ability, the fetal by-products are not adequately dealt with and eclampsia results. From the published observations of Pels-Leusden and Schmorl attention was drawn to the possibility that disturbances in syncytial function could well explain the eclamptic phenomena. Using this as a basis, Veit enlarged the idea to the conception that the cause of eclampsia is the giving off from the

placenta of albuminous material foreign to the host, and an inadequate elaboration of a destructive protective substance "syncytiolysin." Ascoli, Weichardt (*a*)(*b*), Shenk (*a*)(*b*), and Liepmann had varying success in supporting this hypothesis, which was finally and successfully repudiated by the work of Lichtenstein (*a*)(*b*)(*c*), Dryfuss, Freund, Mathes, Wormser, Pollak, and others. In view of his extensive studies on placental enzymes, Hofbauer (*c*) felt justified in advocating the belief that the cause of eclampsia lay in an escape of these enzymes in excess into the maternal blood with subsequent development of toxic products. This hypothesis was supported by Dryfuss, Freund, Mathes, Wormser, Pollak, and others. In view of his extensive studies on placental enzymes, Hofbauer (*c*) felt justified in advocating the belief that the cause of eclampsia lay in an escape of these enzymes in excess into the maternal blood with subsequent development of toxic products. This hypothesis was supported by Dryfuss, Freund, and also by Savaré, who found that autolysis has already commenced in the placenta from eclamptic pregnancies, and that the activity of the desamidases was greater in these placentas than in those obtained from normal pregnancies. It is thus evident that the question of this disease is inherently bound up in the conception of its being an intoxication process, but that the seat of the disturbance, as well as its mechanism, is a matter of speculation and uncertainty. A careful study of all available data was made by Lichtenstein, who, enlarging the idea of Czempin, came to the conclusion that the origin of eclampsia does not lie in the production by the placenta of toxic material *per se,* but that in all probability through a perversion or diminution, or both, of placental function, the fetal metabolic by-products are allowed to escape in quantity into the maternal system, and these being present, in addition to those produced by the maternal organism as the result of its own metabolism, put such additional burden upon the excretory and detoxicating organs that they cannot deal with it and toxemia results. Now Czempin had noted that there was an increased nitrogen in eclamptics, and Farr and Williams, and Slemmons and Morris had also found indications that the urea nitrogen in such cases was increased over the normal, while Hammett (*e*) has demonstrated that not only has the placenta a high urea-forming ability, but that the placentas from pregnancies accompanied by toxemia are much higher in urea content than are those from normal cases. The first group of findings demonstrate clearly that in eclampsia there is an accumulation of unexcreted nitrogenous metabolic by-products, and the latter that the placenta is capable of converting the intermediary nitrogenous products of metabolism into a form normal for excretion. Moreover, unpublished studies of J. L. Bremer on the histological structure of placentas from eclamptic patients seem to indicate that in some placentas at least there has occurred such changes in the syncytium and underlying tissues as

would lead one to suppose the possibility of an increased permeability between fetus and mother. It accordingly appears probable that the cause of eclampsia does not lie in any inherent production of a secretion by the placenta, but rather that this disorder arises from a decrease or perversion, or both, of the intermediary metabolic function of the placenta, accompanied by an increased permeability of the endothelium covering the villi projecting into the maternal sinuses; the combined effect of this increased permeability and decreased detoxicating activity is a flooding of the maternal organism with the incompletely hydrolyzed by-products of the fetal metabolism. This would seem to put such extra burden upon the liver and kidneys of the mother that these tissues are unable to meet the demands upon them, with the result that the subsequent characteristic manifestations of an acute toxemia appear.

The Placenta as a Factor in Growth.—A certain number of direct feeding experiments have been carried on during the past few years, the results of which seem to indicate that when placental tissue is fed to young animals an acceleration of growth results. These investigations, however, present no valid evidence that there is present in the placenta a specific growth-promoting substance, inasmuch as the increased growth observed may well have been due to the addition to the diet of either an optimum supply of ammo-acid precursors, or to an increased vitamin content of the diet. The results of Emmett and Luros, however, show that fat-soluble A vitamin is not a general constituent of the ductless glands.

That certain of the domestic animals commonly consume the afterbirth is well known. Van Hoosen was the first to report an increased growth of breast fed infants when subsisting upon milk produced during the maternal ingestion of desiccated placenta. The plan and scope of her work do not permit the drawing of any definite conclusions, but do seem to show the indications of a tendency. In a study of the effect of the ingestion of desiccated placenta on the variations in the chemical composition of human milk during the first eleven days after parturition, Hammett and McNeile observed that the infants feeding upon this milk made a more rapid recovery from the postnatal decline in weight than infants subsisting on milk uninfluenced by the maternal ingestion of the desiccated placenta, and the assumption was made that there is in the placenta a growth promoting substance, which is passed on to the infants in the milk when placental material is fed to the mothers. Cornell, in a study of the galactagogic action of the placenta, pointed to the possibility that the feeding of such material to nursing mothers has some effect on the growth of breast fed infants. He found that 87 per cent of those infants receiving milk from mothers ingesting desiccated placenta regained their birth weight by the fourth or fifth day, whereas but 67 per cent of those ingesting milk from mothers not receiving this material had reached their original weight during the same period. This augmentation of

growth was attributed to a galactogogic activity of the administered placenta. The evidence from other sources, however, is strongly opposed to the probability of any postpartum stimulatory effect of ingested placenta on milk secretion.

An extended investigation was carried on by Hammett to determine whether or not the maternal ingestion of desiccated placenta would cause

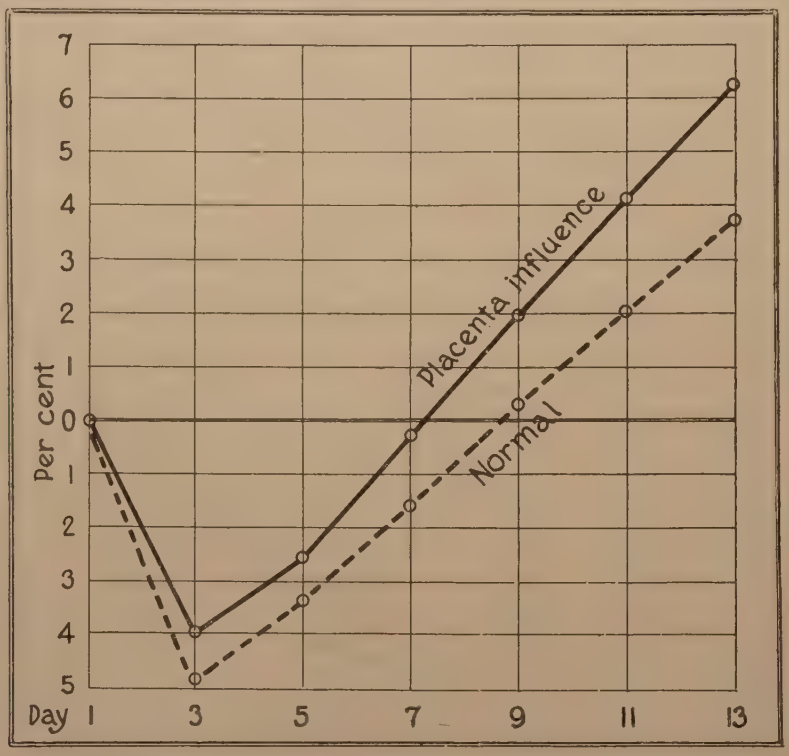

Chart I. Hammett, F. S., J. Biol. Chem. (Balt.), 1918, *36*, 569-573.

an appreciable difference in the rate of growth of the breast fed infants when compared with that observed in normal breast fed infants. The placentas for feeding were obtained from non-luetic and non-gonorrheal women at delivery, immediately ground to a pulp, mixed with 5 to 10 c.c. of toluene and spread in a thin layer over a large glass plate. By means of an air current from an electric fan the material was then dried without appreciable decomposition in about eighteen hours to a leathery semi-brittle mass. This material was then ground as fine as possible and dried for twenty-four to forty-eight hours over sulphuric acid in a vacuum desiccator. Regrinding resulted in a fine dry powder of uniform consistence and a not unpleasant odor. The powder was administered in capsules. As a basis for comparison, the data for normal growth curves

were obtained from the records of 357 infants, born at the Boston Lying-in Hospital, taken on the first, third, fifth, seventh, ninth, eleventh and thirteenth days after delivery, growth data being taken only from the histories of those infants whose sole nourishment was derived from the maternal breast and whose delivery had been normal. Having thus obtained a standard based on the methods of weighing, care, and diet in use at that hospital, every patient was given 10 grains of the desiccated placenta three times a day for two weeks, until a sufficient number of observations had been made, the conditions as to diet, weighing, and so forth being the same as obtained with the cases in which no placenta was fed. The data for calculating the growth curves were obtained from 177 infants on the first, third, fifth, seventh, ninth, eleventh and thirteenth days after delivery. The accompanying chart shows the mean of the percentage change in weight throughout the period of study as regards both sets of infants.

The results of these experiments demonstrated that the ingestion of desiccated placenta by nursing mothers causes an increase in the rate of growth of 60 per cent of the breast fed infants by the thirteenth day, that the postnatal decline in weight is less in amount, and that the growth capacity per unit weight is enhanced. It is accordingly evident that there is produced in the placenta some substance capable of acting as a stimulus to growth when ingested by the mother and passed on in the lacteal secretion to the infant, and it is not illogical to suppose that the placenta *in utero* produces a substance acting as a stimulus to fetal growth. This opinion is justified inasmuch as the food value of the milk was not significantly enhanced and as the total caloric value of the placental material consumed is obviously insufficient of itself to explain the increased weight, even were it all transferred to the milk.

Conclusions

The sum total of the evidence now available justifies the inclusion of the placenta among the endocrin organs. It is to be doubted that the placenta produces a specific secretion concerned in the mammary hyperplasia of pregnancy, and the evidence is cumulatively negative that by any normal secretory process the placenta contributes either to milk secretion or to the etiology of eclampsia. Yet from the data previously recorded and quite recently confirmed by Giesey, that the injection of placental extracts into virgin animals causes a uterine hyperplasia, and from the fact that the rate of growth of breast fed infants is enhanced when they are subsisting upon milk produced during the maternal ingestion of desiccated placenta, the belief is justified that among the placental functions can be included that of producing a growth-promoting hormone.

SECTION IX

The Spleen as an Endocrine Organ. . . . . *F. C. Mann*

Introduction: General Status of the Problem of Splenic Function—The Spleen and the Digestive Function—The Spleen and the Pancreas—The Spleen and the Liver—The Spleen and Metabolism—The Spleen and Its Hemopoiesis—The Spleen and the Lymph Nodes—The Spleen and the Thymus—The Spleen and the Blood—The Spleen and the Blood-Producing Organs—The Spleen in Its Relation to Infection, Immunity and Anaphylaxis—Chemistry of the Spleen—Effect of Extracts of the Spleen—The Spleen and Pathologic Conditions—Conclusions.

The Spleen as an Endocrin Organ

FRANK C. MANN

ROCHESTER

Introduction: General Status of the Problem of Splenic Function

Is the spleen an endocrin organ? It does not seem possible at the present time to answer the question positively. I shall briefly refer to the data and the various theories on the function of the organ and discuss particularly those phases which might warrant classifying the gland as an endocrin organ.[1]

Few organs of the body have played a more important part in literature than the spleen. References to it are so frequent and so contradictory that fact is separated from fancy with difficulty. From the very earliest times the nature of the organ seems to have been a mystery. It attracted the attention of many of the men working in the natural sciences and many indeed are the illustrious names associated with the history of the development of our knowledge of the organ. But the little definite knowledge concerning the spleen which we possess has been difficult to procure. Much of the research on the organ has been barren of positive results or has given rise to numerous false theories. No statement with reference to the function of the spleen has ever gone uncontradicted. All this makes it difficult to evaluate the voluminous evidence with regard to the organ as an endocrin gland.

It is interesting that the same uncertainty attended the meaning of the spleen in poetry as in the scientific consideration of its function. To some poets the spleen stood for mirth, while to others it was used as a synonym for passions, particularly anger (Stukeley, Gray, Black).

The larger number of the various researches on the spleen have dealt with the effect of splenectomy on various organs or functions of the body. The history of splenectomy has been recorded by different authors (Stukeley, Gray, Krumbhaar, Carstens), and a description of its removal in man by Balfour. The spleen was evidently one of the first organs to be re-

[1] Although the dubious position of the spleen in the endocrin congeries is recognized, it seems desirable to present a brief discussion of the evidence, pro and con, of such function.—R. G. H.

moved. It has been known for many years that animals and even man can live without the spleen, and that the loss of the organ produces few changes. The fact that the spleen is not essential to life and good health has been demonstrated on the adult and young of many species.

The Spleen and the Digestive Function

The intimate anatomic relationship of the spleen to the organs of digestion first led observers on the physiology of the spleen to attribute to it an important digestive function. The direct venous connection of the spleen and stomach in all species of vertebrates and their particular relationship in some species of birds call attention to their possible relationship in all animals. Inlow has made an extensive review of the literature on the subject.

Some of the first vague hypotheses concerning the function of the spleen are: The function of the spleen is to draw the watery part of the food from the stomach (Hippocrates); the spleen acts as a prop to the stomach (Aristotle); it keeps the body warm (Galen); and it acts as a heart to maintain a circulation through the stomach (Stukeley).

With the development of experimental methods many investigators, of whom Bacelli is supposed to have been the first, devised methods to test the hypothesis of a functional relationship between the spleen and the stomach. Very contradictory results were obtained (Tarulli and Pascucci, Gallonga, Silvestri (*a*) (*b*), Betti, Gross, Trampedach, Rusca (*a*) (*b*), Soler and Madero).

The most recent work is that of Inlow whose experiments were carried out on dogs. In careful study of the gastric secretion before and after splenectomy it was found that no changes were produced in the quality but the quantity was slightly decreased; this could possibly be attributed to damage of the blood supply of the stomach as has been noted following operative procedures on human beings.

A critical review of all experiments on this question, particularly of the most recent, conclusively shows that a functional relationship between the stomach and the spleen has not been established.

The Spleen and the Pancreas.—The fact that the spleen becomes congested and undergoes marked variation in size during digestion (Leuret and Lassaigne, Dobson, Landois, Dittmar and Vogel) beginning about the time of the pancreatic activity, has led to the belief, first advanced by Schiff (*a*) (*b*) and promulgated by Herzon (*a*) (*b*) (*c*) (*d*), that an internal secretion of the spleen affects the pancreas, but this hypothesis has not been substantiated. Investigations on the subject have been made by Lussana (*a*) (*b*), Gachet, Gachet and von Pachon (*a*) (*b*), Popielski, Besbokaïa, Bellamy (*a*) (*b*), Mendel and Rettger, Frouin (*a*) (*b*), Prym

(*a*) (*b*), Lombroso and Manetta. One of the most interesting observations is that of Sweet and Ellis. They noted that the spleen becomes very small after the external function of the pancreas is destroyed. We have verified this observation. If it can be shown clearly that the atrophy of the spleen following damage to the external function of the pancreas is not dependent on the same factors that cause loss of weight to the rest of the body, an important advance denoting an interglandular relationship of the spleen will have been made.

The Spleen and the Liver.—One of the very early functions ascribed to the spleen is the transformation of the thick and muddy juices generated in the liver (Galen). Since Galen's time more or less vague hypotheses have been advanced concerning an interrelationship of the spleen and liver, the most definite by Black. However, this author gives to the spleen a more or less mechanical function of diluting the blood which passes to the liver, emphasizing of course the importance of Aristotle's observation that the blood from the spleen drains into the portal circulation, and Cuvier's observation that a spleen is present in all species of vertebrates.

Pugliese was the first to study the output of bile pigment from a bile fistula following splenectomy. He noted a decrease of about one-half the pigment while the other constituents of the bile were but little altered. Hooper and Whipple were unable to find any change in the elimination of bile pigment after the removal of the spleen, although very peculiar reactions occurred in the bile pigment of splenectomized dogs when hemorrhage or other experimental complications were added to the removal of the spleen. Such changes did not occur in normal dogs. Goto obtained evidence of a decrease in the elimination of bile pigment after splenectomy and concludes that the spleen influences the formation of the pigment.

Giffin, Sanford and Szlapka have shown that the elimination of urobilin and urobilinogen does not run parallel with the excretion of bilirubin and that when the spleen is removed for pathologic conditions, particularly pernicious anemia and hemolytic jaundice, a very marked decrease in the elimination of urobilin and urobilinogen occurs.

Granting that the spleen exerts some influence on the elimination of bile pigment, this does not necessitate that one postulate the elaboration of a specific internal secretion by the spleen influencing the liver. There is no doubt, as Black first pointed out, that the purely mechanical relation of the spleen to the liver influences the function of the latter. This has been well brought out by a series of studies on the effect of diverting the splenic blood from the liver directly into the general circulation (Krumbhaar, Musser and Peet, Krumbhaar and Musser, Burket). The results of such experiments in general have been identical with those in which the spleen was completely removed from the body, showing the possibility that the spleen acts as a shunt to the portal circulation.

Pathologic studies have long since demonstrated that the spleen and

the liver are often affected by a disorder simultaneously or so nearly simultaneously that it has never been possible to state which organ was involved primarily. However, this does not mean that there is an endocrin interrelationship. It is more probable that the same pathologic cause may be operative in each gland and that a vicious circle is established in which the spleen is the weaker link (W. J. Mayo).

From the evidence submitted, it may be stated that there is some definite interrelationship of function between the spleen and liver, but it seems that all present data on the subject can be explained on a purely mechanical basis. There is no evidence that the spleen elaborates a direct internal secretion which influences the liver.

A résumé of all the extant data on the possible relationship of the spleen to the digestive tract on the basis of an endocrin function leads to the positive conclusion that such a function on the part of the spleen has not yet been proved.

The Spleen and Metabolism

Many investigations have been made of the possible relationship of the spleen to metabolism. Studies have been carried out on the dog and on man, usually of metabolism before and after splenectomy. The experimental work was done on normal animals while the observations on man were associated with some pathologic condition for which splenectomy was done.

Experiments on dogs have involved an investigation of nitrogenous metabolism (Paton, Korenchevski, Goldschmidt and Pearce, King (*b*)); purin metabolism (Mendel and Jackson, King); gaseous metabolism (Verzar, Korenchevski); carbohydrate metabolism (Austin and Ringer, Goldschmidt and Pearce, King); fat metabolism (Goldschmidt and Pearce, King) and mineral metabolism (King). Owing to the fact that the spleen contains a large amount of iron and is closely associated with the breaking down of hemoglobin, the investigation of the mineral metabolism has included several special researches on the relation of the gland to iron metabolism (Schmidt, Asher, Grossenbacher, Zimmermann, Bayer, Austin and Pearce). In most instances no relation between the spleen and the particular metabolism studied could be determined although positive results have been alleged in a few instances. It may be stated, therefore, that the experiments on animals have given no evidence that the spleen elaborates any product which influences metabolism.

Results on the metabolism of patients from whom the spleen has been removed as a therapeutic measure have shown that definite changes sometimes occur (Umber, Mendel and Gibson, Minot, Pepper and Austin, Denis). It should be taken into consideration, however, that the various diseases for which the operation was done had altered the metabolism

of the patient so that the results of splenectomy are not necessarily attributable to a relation of the organ to metabolism.

The Spleen and Hematopoiesis

The Spleen and the Lymph Nodes.—Hewson seems to have been the first to note the anatomic relationship of the spleen to other organs. Since his time numerous investigations have been made, mainly on the lymph nodes, hemolymph nodes, thymus, bone-marrow, and white cells, following splenectomy. The enormous amount of literature which has accumulated on the effect of splenectomy on the lymph nodes has been reviewed by Warthin, Meyer, Pearce, Krumbhaar and Frazier. The results reported are rather conflicting. It can be stated positively, however, that removal of the spleen occasionally produces definite changes in the lymph nodes. Early changes appear to be a hyperplasia of the endothelial cells associated with an increased phagocytosis of these cells for red blood cells. Later the endothelial cells become loaded with blood pigment, and the gland has a reddened or brownish color. In my experiments, gross changes in the lymph nodes have been noted only occasionally, but when they have occurred they were quite marked.

The effect of splenectomy on hemolymph nodes has been reported by Warthin, and their occurrence and distribution have been investigated by Meyer. Warthin studied the hemolymph nodes at various lengths of time after removal of the spleen in goats and sheep and noted the occurrence of a definite hyperplasia. We have examined the hemolymph nodes in six goats after splenectomy at periods varying from nine to four hundred and ninety days. Five of the animals were three weeks old, and one was very old at the time of operation. Only two showed enlargement and hyperplasia of the nodes; in one the changes were very marked. We have not observed hemolymph nodes in the other species of animals such as the dog, cat, rabbit and guinea pig, which we have splenectomized.

The Spleen and the Thymus.—The thymus and spleen have been considered closely related functionally. I have previously reviewed the literature and studied the effect of splenectomy on the thymus in dogs, cats, rabbits, and goats. In general my results were entirely negative. Luckhardt also reports negative results in the rat. The effect of splenectomy on the leukogenic activity of the bone marrow and on the white cells will be discussed with more closely related subjects.

From a review of the mass of data in the literature and from the results of our own studies, it can be stated that splenectomy occasionally produces quite definite, and sometimes marked, changes in the lymphoid structures. These changes seem to be compensatory. They do not appear to be dependent on an internal secretion of the spleen, but rather on the

increased work thrown on the remaining similar structures by the removal of the largest mass of lymphoid tissue in the body, with a resulting hyperplasia and increased activity.

The Spleen and the Blood.—The function of the spleen in relation to the physiology and pathology of the blood is more closely and more clearly defined than that of any of its other alleged functions. For instance, it is definitely known that in fetal and early life, erythrocytes are produced in the spleen. The evidence is also quite strong that the spleen destroys erythrocytes, presumably the old and wornout cells, although experiments dealing with variation in blood counts in the splenic artery and vein are not in accord. A rather extensive review of the literature on this question has been made by Morris (*a*) (*b*), Pearce, Krumbhaar and Frazier.

Splenectomy produces more marked and constant changes in the blood than in any other tissue. These changes have been studied in a large number of researches and in a wide range of species. A few of these studies are by Luciani, Musser and Krumbhaar, Pearce, Austin and Musser, Freytag, Kreuter, Wolferth, Orr and Henn. They involve a study of the blood following splenectomy in normal men (Meyers) and of those from which the spleen had been removed for a pathologic condition (Giffin, Eppinger).

The most constant changes in the blood produced by removal of the spleen are a varying degree of anemia, increased resistance of the erythrocytes, lessened tendency to jaundice following the administration of hemolytic agents, and an increase in the leukocytes. The anemia following splenectomy usually is not marked nor of long duration, reaches its point of greatest severity between the first and second months and returns to normal within three or four months. The hemoglobin curve follows quite closely that of the red cell count. During the process of regeneration, an abnormal type of red blood cell appears in the circulating blood, and nuclear particles have been described (Morris, Roth, Gilbert). It is interesting to note that diet affects the changes in the blood (Pearce, Austin and Pepper).

One of the most constant findings following splenectomy is increased resistance of the erythrocytes to hypotonic salt solution and to hemolytic poison. Almost all of the large number of investigators are agreed on this finding; however, the explanation for it has not been given. The literature is reviewed by Pearce, Krumbhaar and Frazier. The lessened tendency to jaundice following administration of hemolytic agents is a quite constant phenomenon and still not explained.

The results from the effect of splenectomy on the leukocytes are not in accord. Recently the literature on the subject has been reviewed by Orr. Most investigators have noted a definite leukocytosis, relatively high the first twenty-four hours after removal of the spleen, and then gradually

decreasing, although persisting to a slight degree for several months. Giffin notes that leukocytosis is one of the most constant results following splenectomy for pathologic conditions.

The Spleen and the Blood-Producing Organs.—Since removal of the spleen produces definite changes in the blood, it was believed that certain changes might also be found in the blood-producing organs, and such has been noted to be the case. In the most recent article dealing with the subject, by Pearce and Pepper, an extensive review of the literature appears.

Johnstone, who has studied the blood for kala-azar following splenectomy in man, is now studying the problem in my laboratory. Controlling one dog against another, he found it impossible to obtain consistent results. A technic was devised, therefore, of removing and studying bone-marrow of a rib at various intervals following removal of the spleen. A few of the rather definite results are briefly as follows:

Immediately after splenectomy leukogenesis is very active and reaches its maximum activity quickly. In from one to three months it decreases until it has resumed its preoperative degree of activity, or is even below this. In about one-half of the animals there is a preliminary period in which erythrogenesis seems dormant. It then becomes more and more active until it exceeds the preoperative degree of activity. In the other half of the animals erythrogenesis begins almost immediately after splenectomy, but so slowly that it is difficult to detect. In either instance, it usually reaches its maximum in from three to four months, remains stationary for two months longer, and then gradually decreases. It is interesting that the marrow findings correspond to the blood picture after splenectomy.

It is difficult to postulate the relationship of the spleen to the blood and the hematopoietic system. That there is some relationship is beyond doubt. The evidence is not complete, however, to show that such a relationship is maintained by the intermediation of an internal secretion of the spleen.

The Spleen in Its Relation to Infection, Immunity, and Anaphylaxis

The spleen has been considered related to infection, immunity, and anaphylaxis. Here again the data from the various experiments do not harmonize. While the spleen undoubtedly acts in a measure as a bacterial filter, experiments have shown that the kidney serves this purpose quite as well or better (Ozaki (*a*) (*b*)). It is still debatable whether the spleen plays an important rôle in immunity, whether bacteria (Lewis and Margot (*a*) (*b*) (*c*), Murphy and Ellis), tumor (Murphy, Morris, Woglom, Ste-

venson, Biach and Weltmann, Bullock and Rohdenburg), or some constituents of the blood which seem to be associated with immunity are involved (Karsner, Amiral and Bock, Kolmer and Pearce). Some part in the production of anaphylaxis has been attributed to the spleen (Mautner); Sanford and I, however, have been unable to note any difference between the anaphylactic phenomenon due to horse-serum in normal guinea pigs and in guinea pigs from which the spleen had been removed at different periods before the production of the anaphylactic phenomenon. At any event final evidence of the part the spleen may play in infection, immunity, and anaphylaxis can be explained on the basis of a purely mechanical action of the gland, and its being the largest reservoir of lymphocytes in the body.

Chemistry of the Spleen.—The chemistry of the spleen which has been reviewed by Corper and others has been shown to be rather complex. It is supposed to have some relation to the fatty acids (King), but this has been denied (Dubin and Pearce). Also a change in the phosphorus in the corpuscles has been noted after splenectomy (Donati).

Effect of Extracts of the Spleen.—Studies on the various extracts of the spleen have on the whole given negative results. Fresh or raw splenic tissue has been fed without producing any noteworthy effects. One of the positive results obtained is the marked increase in the tonus and pendulum movements of the isolated intestine (Ott and Scott, Grube, Berlin).

The Spleen and Pathologic Conditions.—As was previously stated, some of the pathologic conditions of the spleen are closely associated with pathologic conditions in other organs. This gives a pathologic basis for the fact that some clinical findings suggest an interrelationship between the spleen and other organs. Clinical evidence is lacking, however, to justify the conclusion that the spleen is an endocrin organ (Giffin).

Conclusions

No statement concerning the function of the spleen has gone uncontradicted. This should not be interpreted to mean that false or incorrect data have been obtained, or that too extravagant conclusions have been drawn, but that the function of the spleen is more or less passive in nature and vicarious in its action. Our data emphasize this point. For instance, the change in the blood following splenectomy seems to be the most constant result obtained. Yet in some of the dogs in our series subjected to splenectomy, no anemia occurred; in others there was no increase in the resistance of the red cells and in still others a leukocytosis other than that which could be definitely attributable to the operative procedure itself did not occur.

It might be expected that if a reaction was produced by splenectomy in any tissue, it would be produced in the accessory splenic tissue, often

noted in many species of animals. As usual, contradictory literature has been developed on this question (Meyer). In a large series of dogs we have studied the effect of splenectomy on accessory spleens. In many cases no changes in the accessory spleen were noted, while in others an enormous increase in size occurred. This illustrates again the vicariousness of the spleen.

At present there seem to be but two positive statements that can be made with regard to the function of the spleen.

1. As the largest lymphoid organ in the body, it has the function of lymphoid tissue in general. Whether or not the few definite and rather constant changes occurring in the hematopoietic system after splenectomy can be attributed wholly to the loss of this mass of lymphoid tissue cannot be stated. Such, however, would be the most probable explanation.

2. The spleen has some function in relation to the portal system. Whether or not this is purely mechanical, whereby arterial blood is shunted through to the liver without becoming mixed with the products of digestion, cannot be stated, but there is much evidence to make this appear true. It is readily seen that for the two more or less definite functions that can be ascribed to the spleen, it is not necessary to refer to an intermediary in the form of an internal secretion.

In conclusion it may be stated that while there is a possibility that the spleen may elaborate a true internal secretion, there is at present not enough evidence to warrant its classification as an endocrin organ.

SECTION X

The Internal Secretion of the Liver and Its Disorders

Charles W. Hooper

Introduction—Significance of the Liver in the Bodily Economy—Substances Contributed by the Liver to the Blood—Carbohydrate as a Hepatic Internal Secretion—Carbohydrate Metabolism After Eck Fistula—Hemoglobin Antecedents as Hepatic Internal Secretions—Bile and Hemoglobin Formation—Blood Serum Proteins as Hepatic Internal Secretions—Origin of Blood Serum Proteins—Substances Involved in Anaphylaxis as Hepatic Internal Secretions—Anaphylaxis and Antithrombin—Antithrombin as a Hepatic Internal Secretion—Pro-antithrombin and Heparin as Hepatic Internal Secretions—Fibrinogen as a Hepatic Internal Secretion—Urea as a Hepatic Internal Secretion—Evidence of Internal Secretion from Administration of Hepatic Substance and Derivatives—Liver Substance—Cod Liver Oil—Liver Extracts—Conclusions—The Place of the Liver in the Endocrine Congeries.

The Internal Secretion of the Liver and Its Disorders

CHARLES W. HOOPER

NEW YORK

Introduction—Significance of the Liver in the Body Economy

The progress of experimental methods has fully demonstrated the great importance of the liver both as a gland of internal secretion and as a protective organ against injurious metabolites and extraneous poisons. The liver is an immense fort stationed between the portal and systemic circulations ready for service in any emergency. It withstands attack and injury and restores itself with astounding rapidity. Prolonged chloroform anesthesia may destroy one-half or more of the liver parenchyma in every lobule and yet, under favorable conditions, the liver may undergo complete repair in from eight to ten days. Davis, Hall, and Whipple (1919) estimate that the human liver, after severe chloroform injury, followed by a carbohydrate rich diet, is capable of constructing a mass of liver cells, 100 to 150 gm. every twenty-four hours, equal in size to the normal spleen or kidney.

The liver contains an abundance of active tissue. However, the generally accepted view, based on Ponfick's observations (1889-90), that one-fourth the liver mass contains sufficient parenchyma for normal requirements is not conclusive in the light of later experiments. Von Meister (1894) found that, after partial ablation of the liver in rabbits, the remaining liver mass attains the weight of the whole liver in from forty-five to sixty days. Ponfick (1895) demonstrated that this compensating hypertrophy begins within three days. Rous and Larimore (1920) observed in rabbits that the liver atrophy following the occlusion of portal branches of a part of the liver is dependent upon a compensatory hypertrophy of the remaining hepatic tissue. They state that three-fourths of the liver may be reduced to a fibrous tag within three months, during which time the remaining fourth may attain the bulk of the entire organ.

Substances Contributed by the Liver to the Blood

Carbohydrate as a Hepatic Internal Secretion.—*The Formation and Discharge of Glycogen.*—Claude Bernard (*a*) in 1848 observed that animals, like plants, have the power of forming sugar independent of the nature of food, and stated that this new function resides in the liver. He suggested that the formation of sugar by the liver is a chemical process directly influenced by the nervous system. He found that the blood of the right heart contained sugar, not only when extracted from a dog fed on sugar, but also when the animal was on a meat diet. Extract of liver was able to reduce Barreswil's reagent and gave rise to alcoholic fermentation. From this he concluded that the liver was the organ capable of forming sugar, independent of that ingested. In 1853 he stated that he had demonstrated the presence of sugar in the liver of mammals, birds, reptiles, fishes, and molluscs. He further proved that the blood of the hepatic veins invariably contained sugar during digestion; that it contained less when digestion was completed; hardly any after a long fast. After prolonged feeding of dogs with meat he failed to find sugar in the intestine or in the portal blood. In the hepatic veins and in the liver he found considerable amounts.

In 1855 Bernard established his theory of internal secretion: That the liver has two functions of secretion; external secretion, which produces the bile which flows to the exterior; internal secretion, which forms sugar which enters immediately into the blood of the general circulation.

Hensen (1857) and, shortly after, Bernard (1857) extracted glycogen from the liver. Bernard then modified his original belief concerning the direct formation of sugar in the liver and stated that glycogenesis is indirect and consists of two distinct processes: amylogenesis, the formation of glycogen in the living liver tissue and glycogenesis proper,—the conversion of glycogen into sugar by an enzyme. The fact that the conversion of glycogen into sugar is arrested by heating freshly excised liver tissue in boiling water convinced Bernard that glycogenesis proper (glycogenolysis) is dependent upon a hepatic diastase. In 1877, by extraction with glycerin he obtained from the liver an enzyme which converts glycogen into sugar. Pavy (1894) extracted from the liver an enzyme which determined the conversion of glycogen into glucose. These results were subsequently confirmed by Tebb in 1897 and others. It is probable, therefore, that the normal conversion of glycogen to dextrose is affected by special enzymes produced in the liver cells. Bernard believed the formation of sugar in the liver to be controlled by the nervous system. In 1858 he found that puncturing the floor of the rhomboidal sinus near the apex of the calamus scriptorius was followed by a marked hyperglycemia and

eventually by glycosuria. He also found that reflex excitation of the bulbar center sufficed to produce the same phenomena.

The importance originally attributed to the diabetes puncture, as discovered by Bernard, gradually diminished as the result of later experiments. Now it is generally accepted that there is no diabetogenic center and that abnormal excitation of any important part of the nervous system may directly or indirectly provoke glycosuria.

Glycogen, which arises principally from the carbohydrates of foods, functions as a reserve material analogous to vegetable starch, which plants use as a source of energy. That the glycogen content of the liver depends essentially on the diet, has been clearly demonstrated by the fact that during an absolute fast it almost entirely disappears from the liver (see Pflüger (*a*) (*b*), 1903-05).

The liver is not the sole organ concerned in glycogen formation. Bernard (*g*) (1859), Nasse (1869) and many others have demonstrated glycogen in the muscles. Külz (1890) found that the muscles also are capable of fixing sugar and converting it into glycogen. Macleod and Funk (1917) compared the sugar retaining ability of the liver and muscles during the injection of moderate amounts of dextrose into the portal vein and found that the sugar retaining power of the voluntary muscles is approximately equal to that of the liver. Their experiments are opposed to the generally accepted opinion that the liver removes from the portal blood all the excess of sugar added to it by intestinal absorption. Furthermore, Vezár (1911) and others agree that the liver may not be necessary for the burning of carbohydrate. This view is also confirmed by Eck fistula experiments.

The constant presence of glycogen in the liver of dogs, fed for a long time on an exclusive meat diet, indicated to Bernard that part of the hepatic glycogen came from the alimentary proteins. Rolly (1905), Pflüger (1907), Pflüger and Junkersdorf (1910) and many others, by starvation experiments on animals, have shown that the liver continues to form glycogen, probably at the expense of the body protein, by cleavage of the protein molecule. Pollak (1909) demonstrated that fasting rabbits, and also those made glycogen-free by the administration of strychnin, can by small increasing doses of epinephrin be made to store liver-glycogen in a quantity only equaled in carbohydrate fed animals. But the muscles remain entirely or almost devoid of glycogen. Reilly, Nolan and Lusk (1898) showed that dogs with severe phlorhizin diabetes continued to excrete sugar, even when fed on protein alone or when starved. They obtained a definite dextrose nitrogen ratio in the urine D : N : : 3.75 : 1, which would indicate a sugar production from protein of nearly 60 per cent. Dakin (1913) furnished direct evidence that some of the amino-acids yielded by proteins may serve as a starting point for the formation of glycogen.

Glycogen may also arise from the decomposition of the fat molecule.

The formation of carbohydrate from fat is demonstrated in the germination of fatty seeds, where starch and cellulose are formed from fat (see von Sachs, 1887). Cremer (1902) and Lüthje (1904) have furnished proof that glycerin may be converted into glycogen. They observed that when glycerin was administered to depancreatized dogs, glycosuria increased approximately in proportion to the dose. Corroborative evidence is also furnished by the very low respiratory quotient during hibernation. The experiments of Dubois (1896), Pembrey (1903) and Weinland and Riehl (*a*) (*b*) (1907-08) suggest that a conversion of fat into glycogen takes place, and that the glycogen is used up as combustion material during the process of awakening. However, Krogh (1916), who has reviewed the subject thoroughly, states that there is no satisfactory evidence of glycogen formation during hibernation, but that such a formation takes place cannot be denied. Furthermore, Mandel and Lusk (1903) found no increase in the urinary sugar in a dog with phlorhizin diabetes when given 100 gm. of fat; and Lusk (*a*) (1908) also observed that active muscular work, which undoubtedly increases the fat decomposition, does not change the D : N ratio in phlorhizinized dogs.

Other arguments in favor of the formation of a part of the glycogen in the body from decomposition of proteins, or possibly from fat, can be substantiated by clinical experience with human beings suffering from diabetes (see Allen (*b*), 1916-17). In the acute form of diabetes in man, there is a complete loss of power to oxidize the carbohydrate material of the food and it is excreted unchanged in the urine, which is evidence that the organism under these conditions must exist at the expense of the protein and fat.

In view of the voluminous researches on diabetes mellitus, it would be impracticable even to attempt a review of the literature dealing with the various hypotheses in which the liver plays a prominent part (see Allen, (*a*), 1913). All the evidence militates strongly against the liver as the only organ concerned in the metabolic disturbance in diabetes. It is probable that the hyperglycemia and glycosuria, which represent the main symptoms of this disease, depend on a lowered glycolysis in which the diabetic organism has lost its normal capacity for burning the sugar as it is formed. Nevertheless, the great importance of the liver as a storehouse of glycogen, as a regulator of the sugar of the blood and its numerous other activities in general metabolic processes should not be cast aside without due consideration in the study of this most baffling disease.

Carbohydrate Metabolism After Eck Fistula.—Many investigators have studied the carbohydrate metabolism in Eck fistula dogs. Glycosuria has never been observed. De Filippi (*a*) (*b*) (*c*) (1907-08) carefully studied this question in special relation to the theory of Claude Bernard on the glycogenetic function of the liver. The tolerance for levulose was markedly reduced, but that of dextrose only slightly. Such a dog may show the

muscle-glycogen content characteristic of an overnourished dog, and the liver-glycogen content characteristic of inanition. The author concluded that the muscles form glycogen and compensate for the loss of liver function in regard to glycogenesis. Hawk (1908) failed to find glycosuria following the ingestion of carbohydrate food. Macleod (1908) established Eck fistulæ and did not observe glycosuria and later clamped the portal vein for short intervals. Hypoglycemia but not glycosuria was found to result. Michaud (1911) found that the Eck fistula prevents epinephrin glycosuria and also observed that the blood sugar remains normal or increases within normal limits after the ingestion of 100 gm. dextrose. Bernheim and Voegtlin (1912) found the carbohydrate tolerance only slightly reduced. Sweet and Ringer (1913) state that after the administration of phlorhizin glycosuria follows, resembling in every detail that observed in normal dogs. This is contrary to the findings of Rosenfeld (1907), who did not obtain any glycosuria at all. McGuigan and Ross (1915-16) found that the utmost conceivable uncomplicated change in the circulation of the liver can play but a minor rôle in the production of glycosuria or diabetes. Jacobson (1920) concludes that glucose tolerance is only slightly modified in Eck fistula animals, while the levulose tolerance is extremely low. The liver is essential for levulose metabolism, but not entirely essential for glucose metabolism. The muscles perform well the functions of glycogenesis and glycogenolysis when the liver is shunted out of the portal circulation.

Hemoglobin Antecedents as Hepatic Internal Secretions

Bile and Hemoglobin Formation.—Voegtlin and Bernheim (*a*) (1911) conclude that the jaundice and fatal toxemia resulting from occlusion of the common bile duct can be avoided by an Eck fistula made at the time of the ligation of the common bile duct. The amount of bile formed depends on the blood flow through the liver and on the fact that the liver has a hemolytic function. Whipple and Hooper (*a*) (1913) have shown that simple obstruction of the common bile duct when combined with an Eck fistula gives rise to a definite low grade icterus with bile pigments constantly present in the urine. The formation of bile and bile pigments is much less in an Eck fistula dog than in a normal animal, and, consequently, the icterus is much less intense. They attribute this to a lessened activity of the liver cells because of decreased blood supply and suggest that the bile pigment may be formed in part from other substances than hemoglobin; further, that normally bile pigment formation may depend in part upon the functional activity of the liver cell rather than upon the amount of hemoglobin supplied to it. Furthermore, they show that normal and Eck fistula dogs react in a similar manner to the intravenous injection of

hemoglobin and to the hematogenous jaundice produced by chloroform anesthesia. In 1917 they found that the Eck fistula liver secretes from one-third to three-fourths the normal amount of bile pigment. Splenectomy added to the combined bile and Eck fistula does not essentially modify the result. Also, they have found that the simple bile fistula and the combined bile and Eck fistula dogs show the same histological picture in the hematopoietic system. This indicates that bile pigment formation is in part dependent upon liver function and not solely upon red cell disintegration. Possibly the production of hemoglobin may depend in part upon the constructive capacity of the liver. Hooper and Whipple (*c*) (1917) reported experiments which show that the Eck fistula liver can eliminate hemoglobin from the blood stream as promptly as the control liver. Even with a high red count the color index will often be low in the Eck fistula. This is evidence that the Eck fistula animal has a subnormal pigment building capacity. The Eck fistula dogs show periods of anemia, which may be referable to an inadequate supply of prepigment material manufactured in the liver. The anemia after bleeding is much more severe and the following period of blood regeneration is much longer than that of normal dogs. Combined Eck and bile fistula dogs show less tendency to develop icterus with bile pigments in the urine than do the simple bile fistula dogs. Apparently the Eck fistula liver can excrete the pigment radical of hemoglobin as promptly as the normal liver. Bile pigment and hemoglobin formation can be controlled at will by diet. These facts overthrow the long accepted theory that bile pigment is formed only as the result of the disintegration of red cells; and they furnish direct evidence that the liver may construct a prepigment material which may be utilized as a true internal secretion to construct prehemoglobin and hemoglobin as needed by the red cells, while the excess reserve supply which is not needed in the body economy is excreted in the bile as bile pigments.

Blood Serum Proteins as Hepatic Internal Secretions

Origin of Blood Serum Proteins.—Seitz (1906) stated that the liver may act as a storehouse for serum proteins. Grenet (1907) and Gilbert and Chiray (1907) found the serum proteins decreased in clinical cases of liver insufficiency. Kerr, Hurwitz and Whipple (1918) presented experimental evidence that the liver may be concerned in maintaining the normal level of the blood serum proteins. Eck fistula dogs show a distinct inability to regenerate blood serum proteins following plasma depletion. Pronounced injury of the liver by means of phosphorus or chloroform will be associated with moderate fall in blood serum proteins. Regeneration of blood serum proteins following plasma depletion will be delayed by the presence of liver injury. These experiments indicate that liver insuffi-

ciency may impair the normal emergency reproduction of blood proteins. Additional experiments of Whipple, Smith and Belt (1920) indicate that the blood serum proteins are stabilizing or protective factors. These observers state that such proteins are essential environmental factors of the circulating blood in its relation to the body cells and that this may be the most important function of these plasma colloids. Other experiments by the authors indicate that the liver cells are particularly concerned in the shock reaction which follows plasmapharesis. A fatal shock reaction is almost constant following even moderate plasma depletion preceded by liver injury. This would indicate that the liver cells are particularly concerned in the shock reaction which may follow plasmapharesis and lowering of the blood plasma protein values. It may be that this type of shock is not unlike the common surgical shock. The evidence in their experiments also gives strong support to the theory that in shock there is a primary cell injury which precedes the familiar clinical reaction.

Substances Involved in Anaphylaxis as Hepatic Internal Secretions

Anaphylaxis and Antithrombin.—Manwaring (*a*) (*b*) (1910), in experiments on the mechanism of anaphylactic shock in dogs, demonstrated that in the absence of some of the abdominal organs, especially the liver and the intestine, shock cannot be produced. It was pointed out that the pronounced fall of blood pressure, which is the essential feature of the acute anaphylactic reaction in dogs, is not due to the direct action of a foreign protein on the sensitized blood vessels, but is an indirect phenomenon, due to the explosive formation or liberation of depressor substances by the liver. Voegtlin and Bernheim (*b*) (1911), working with Eck fistula dogs, conclusively demonstrated that the liver is essential for the development of anaphylactic shock. This fact has been confirmed by Denecke (1914) and renders certain that the liver is essential for the vasomotor depression, inasmuch as the latter fails to supervene if the liver is excluded from the circulation.

In the guinea pig the vasomotor disturbance plays a small part in the acute shock of anaphylaxis, but in its stead there occurs a spasmotic closure of the bronchioles by their circular musculature, with inspiratory fixation of the lungs and asphyxia. Manwaring and Crowe (1917) and Rumpf (1918) submit experimental evidence which tends to show that the liver may also be concerned in the development of anaphylaxis in guinea pigs.

Weil (*b*) (1917) has shown that peptone affects the liver in exactly the same fashion as anaphylaxis. The isolated organ, when perfused thereby, renders the blood incoagulable. Injection into one branch of the portal vein induces a localized area of hepatic congestion. It is also emphasized

that human beings with serum sickness not infrequently show low blood pressure, and diminished coagulability of the blood. Guinea pigs also give evidence of diminished coagulability, indicating hepatic involvement in the anaphylactic response. The author also infers that the results introduce a new function of the liver, namely, its participation in the immune reaction.

Pearce and Eisenbrey (1910) demonstrated conclusively that anaphylactic sensitization is manifested mainly in the tissue cells, rather than in the circulating blood. They found that a sensitized dog, transfused with normal blood, exhibits immediate anaphylactic shock when the antigen is injected; whereas a non-sensitized dog transfused with sensitized blood, shows no immediate effect when the antigen is injected. It is also proved by the experiments of Schultz (1910), Dale (1912) and Weil (*a*) (1914), that excised and blood-free organs of sensitized animals exhibit a high specific response to the sensitizing protein. According to Weil (1917), the site of the cellular reaction in dogs is the hepatic parenchyma. Other tissues may participate, but at present there is nothing to indicate that this is the case. In the guinea pig the chief site of the cellular reaction is the smooth muscle tissue. The fact that in both species the fundamental mechanism is a cellular reaction, even though different tissues are involved, furnishes the basis for a uniform theory of anaphylaxis. The fact that peptone affects the liver in very much the same manner as does a specific antigen to which the organ is sensitized, may serve to explain the therapeutic effects observed after the injection of this substance in certain infections, such as typhoid fever.

It is well established that the coagulability of the blood is markedly diminished during anaphylactic shock in the dog. Coagulation may be only delayed, or it may be completely abolished. According to Weil, a similar change, though slighter in degree, characterizes the blood of rabbits in anaphylaxis and of guinea pigs in case the shock is protracted.

Antithrombin as a Hepatic Internal Secretion

Delezenne (1898), Popielski (1913), and others, have shown that peptonization in the dog causes a notable augmentation of the antithrombin in the blood and state that it is produced in the liver. This conclusion is corroborated by the experiments of Denny and Minot (1915). Long stasis of blood in the liver, as well as perfusion of the organ, was accompanied by a distinct increase in the antithrombin content, results which are not obtained from other organs. Destruction of liver tissue, as in phosphorus poisoning, occasions on the contrary a marked decrease in antithrombin.

Howell (*a*) (1914) devised an accurate method for testing the relative

amount of antithrombin in the blood. In hemophilia the antithrombin may be normal or somewhat increased. In spontaneous thrombosis of the veins the antithrombin is diminished, and in purpura hemorrhagica, and in other forms of so-called purpura, no evidence was found of any variation from the normal. Drinker and Drinker (1915) found that rapid progressive hemorrhage in animals causes a progressive shortening of the coagulation time, and a parallel or greater diminution in antithrombin. Minot, Denny and Davis (1916), using Howell's method, have also studied quantitatively the antithrombin in various pathological conditions in man. A positive increase in antithrombin content of the blood is indicated in three cases only, namely, acute splenomyelogenous leukemia, aleukemic leukemia and congenital hemophilia. Diminution in antithrombin was found especially in cases of severe typhoid fever, certain leukemias, anemias and thrombosis.

The majority of authors agree that antithrombin plays the important rôle of protecting the blood from clotting within the vessels. Before drawing a definite conclusion that antithrombin, as such, is an internal secretion of the liver one should review briefly the recent work on blood coagulation. A survey of the results indicates that at least eight different substances are concerned in one way or another in the process; namely, fibrinogen, thrombin, heparin, prothrombin, calcium, pro-antithrombin, antithrombin, and the so-called zymoplastic or thromboplastic substances (cephalin) furnished by the tissue cells in general, including the blood corpuscles.

Pro-Antithrombin and Heparin as Hepatic Internal Secretions

These two substances have been described by Howell (*b*) (1916-17) and by Howell and Holt (1918). They designate pro-antithrombin as the antecedent or mother substance, present in blood plasma or blood serum, from which antithrombin is formed by a reaction with heparin. By a reaction analogous to the activation of prothrombin to thrombin by calcium, the pro-antithrombin is activated to antithrombin by heparin. Heparin is described as a phosphatid which exists in various tissues, but is found most abundantly in the liver. It possesses two characteristic reactions. First, it retards or prevents the coagulation of the blood, both in the body and when the blood is shed, mainly by preventing the activation of prothrombin to thrombin. In this respect it acts as an antiprothrombin rather than as an antithrombin. Second, it causes a marked increase in antithrombin when added to blood or serum by activating the pro-antithrombin to antithrombin.

On the theoretical side, Howell and Holt suggest that heparin and pro-

antithrombin are normal constituents of the circulating blood and together fulfill the function of safeguarding the fluidity of the blood; that is to say, of preventing intravascular clotting. The pro-antithrombin by its conversion to antithrombin provides a protection against any small quantities of thrombin that may arise in the circulating blood. The heparin in addition to functioning as a specific activator to pro-antithrombin exerts an inhibiting influence upon the conversion of prothrombin to active thrombin. When blood is shed or when in other ways thromboplastic substances (cephalin) are added to the blood, the protection afforded by the heparin is overcome and thrombin is formed in amounts sufficient to cause clotting. It is also suggested that variations in the amount of heparin in the blood may suffice to explain some of the known abnormalities in coagulation,—hemophilia, for example. Blood to which heparin has been added in amount sufficient to cause a marked slowing of the time of coagulation, presents a picture which is identical with that exhibited by hemophilic bloods. There is the same prolongation of the time of spontaneous coagulation, the same retardation in the prothrombin time and the same tendency toward an increase in antithrombic action.

Addis (1911) presented experimental proof that the hemophilic condition is due to a retardation in the activation of prothrombin to thrombin, corresponding in degree to the delay in the coagulation of the blood. However, he failed to find a substance in hemophilic blood, not present in normal blood, which hindered the activation of prothrombin and attributed the condition to a qualitative defect in the prothrombin itself. Howell (1914) and Hurwitz and Lucas (1916) have also shown that the characteristic peculiarity of hemophilic blood is its markedly delayed time of coagulation, which they attribute to a diminution in amount of the prothrombin resulting in a relative excess of antithrombin. Howell and Holt's suggestion in 1918 that the condition of hemophilia may be due to an abnormal amount of heparin in the blood, should be submitted to experimental examination as soon as an adequate method is devised for the estimation of heparin in circulating blood.

Fibrinogen as a Hepatic Internal Secretion

Fibrinogen is a globulin-like body present in the normal blood in fairly constant amounts; it may be considered as an internal secretion elaborated by the liver. It gives rise to an insoluble protein, fibrin, the formation of which is the essential phenomenon in the coagulation of blood, in that it forms the body and main bulk of the clot. If this substance is reduced in the blood there is no abnormality in the process of blood-clotting, but the formed clot is more or less flabby, depending on the amount of reduction. Jacoby (1900), Doyon, Morel and Kereff (1905)

and Whipple and Hurwitz (1911) and others have shown that the fibrinogen of the blood may be reduced to a very low level by poisoning with phosphorus or chloroform. Whipple (*a*) (1912) has shown that when the fibrinogen is present in only small amounts in the circulating blood, extensive hemorrhages may be observed from small wounds in the skin, oozing from the mucous membranes and purpura. This drop in blood fibrinogen is invariably associated with extensive injury to the hepatic tissue, usually with extensive necrosis of the liver cells. Observations on dogs suffering from acute liver injury (chloroform) with hepatic insufficiency, and parallel observations on human cases of cirrhosis, with progressive hepatic insufficiency, prove beyond doubt that the liver is the essential factor in maintaining the normal fibrinogen balance of the blood.

Meek (*a*) (*b*) (1912) noted that after an Eck fistula, ligation of both portal vein and hepatic artery and partial defibrination, fibrinogen is no longer reformed, and that the amount remaining in the blood rapidly disappears. In the normal dog it is regenerated at a rapid rate after partial defibrination. In three hours the amount may be increased as much as 100 per cent. From this he concluded that the liver itself forms fibrinogen. Whipple (*b*) (1914) and Goodpasture (1914) are of the opinion that normal fibrinogen production is the result of the combined activity of the liver and the intestine. However, they admit that the intestine is not essential to fibrinogen regeneration, but it is an important contributing factor in its rapid formation.

Experimental evidence conclusively indicates that fibrinogen is formed in the liver, and that this organ is the essential factor in maintaining the normal fibrinogen balance of the blood.

Urea as a Hepatic Internal Secretion

The complete story of urea formation in the body is not entirely known. Present knowledge indicates that the main bulk of urea is formed in the liver. It is then given to the blood as an internal secretion and finally excreted by the kidney. Schröder (1882) established an artificial circulation in the excised dog liver, and made a chemical analysis of the blood before and after it passed through this organ. He found that blood taken from well fed dogs showed a distinct increase in urea after passing through the liver, while blood from fasting dogs showed no change. Blood from well fed animals showed no increase after being circulated through the isolated kidney or muscle. Further, he showed that if ammonium carbonate was added to the blood circulating through the liver it was converted into urea. This conversion is affected by the liver cells by a process equivalent to dehydration, in which the ammonium carbonate loses water and is converted into urea. The experiments of Hahn, Massen, Nencki and

Pawlow (1893) with Eck fistula dogs, also show that the liver protects the body from the poisonous action of the ammonia compounds formed in the normal digestive hydrolysis of proteins by converting them into urea.

Most of the protein nitrogen in the daily diet of an adult is excreted within twenty-four hours as urea. Levene and Kober (1909) found that when single amino-acids were fed to dogs they were excreted entirely as urea. The experiments of Van Slyke and Meyer (1913) point to the liver as the organ which is most active in absorbing amino-acids from the blood stream during normal digestion, and in submitting them to the chemical alterations which precede elimination as urea, or storage as reserve protein. Amino-acids injected into the circulation are absorbed by all tissues: those taken up by the liver disappear rapidly. The amino nitrogen content of this organ may be doubled by an injection of amino-acids into the general circulation, and yet return to normal within two or three hours. During the period required by the liver to rid itself entirely of absorbed amino-acids, no appreciable diminution has occurred in that stored in the muscles. From other organs they disappear less rapidly than from the liver. The disappearance of the amino-acids from the liver is accompanied by an increase in the urea of the blood. Van Slyke, Cullen and McLean (1915) operated on dogs at varying intervals after feeding, and found the urea content of the blood from the hepatic vein 3 to 20 per cent higher than that of the portal blood. A similar increase in the urea content during passage of the blood through the muscle tissue did not occur. Van Slyke (1916) presents sound experimental proof that the blood in passing through the liver takes from it about as much nitrogen in the form of urea, as it gives to it in the form of amino-acids.

It is generally agreed, therefore, that the liver deaminizes the greater part of the amino-acids and is the organ most concerned in the synthesis of urea. However, urea formation is not a process entirely confined to the liver. Kaufmann (1894), Nencki and Pawlow (1897) and Fiske and Summer (1914) have proved that dogs may still form urea to some extent when the liver is excluded from the circulation.

Evidence of Internal Secretion from Administration of Hepatic Substance and Derivatives

Liver Substance.—Rapid emaciation, malnutrition and anemia of dogs with biliary fistulæ, and the eagerness of the animals to lick the bile from the fistulæ, all suggest the need of this body fluid. The experiments of Hooper and Whipple (*a*) (1916) indicate that bile is essential for the life of an animal on a mixed diet of meat, bones and bread. If bile is wholly excluded from the intestinal tract, the dog loses ground steadily, shows intestinal disorders, accompanied by blood in the feces,

and usually within a very few weeks dies of peculiar symptoms of intoxication. Administration of bile may improve the condition temporarily. However, liver feeding is of peculiar benefit and may maintain the animals in normal condition for many months. Unpublished experiments by Foster and Hooper indicate that the substance in the liver responsible for this influence on the abnormal metabolism of bile fistula dogs is present in either jecorin or heparphosphatid. Hooper and Whipple (*b*) (1917) have shown that bile fistula dogs after splenectomy may also remain in normal condition for months and even years. However, eventually these animals show periods of spontaneous icterus, blood destruction and high bile pigment output, which may terminate fatally with bleeding from the gums and the gastro-intestinal tract. Regeneration of red cells with consequent recovery from experimental anemia, induced by bleeding, is very greatly prolonged and may occupy months in splenectomized animals, as compared with weeks in simple bile fistula dogs without splenectomy. The color index may remain high during the long period of blood regeneration in the splenectomized dogs. The output of bile pigments may average considerably above normal, which may indicate an overproduction of blood and bile pigments with perhaps a deficiency of red corpuscle stroma. These experimental data strongly suggest an interaction of the liver and spleen in the construction, as well as the destruction of hemoglobin and red cell stroma.

That the liver may be concerned in the warehousing and metabolizing of food hormones or vitamines, is suggested by certain feeding experiments. Cooper (1914) studied the efficiency of various ox tissues in postponing the development of polyneuritis in pigeons on a diet of polished rice. The tissues arranged according to their antineuritic powers are in the following descending order: liver, cardiac muscle, cerebrum, cerebellum, voluntary muscle, and (cow's) milk. Osborne and Mendel (*b*) (*c*) (1917-18) demonstrated that liver not only contains a large proportion of water-soluble vitamin, but also adequate protein and sufficient fat-soluble vitamin to maintain normal growth in rats. The authors also show that pig liver oil contains growth promoting properties comparable with those of butter fat and cod liver oil.

Cod Liver Oil.—Aside from its very high food value and the fact that it has already been desaturated by the liver of the cod and prepared for the metabolic processes in which fat is concerned, cod liver oil has been shown experimentally to contain substances which play a vital rôle in promoting normal growth and bone formation.

Osborne and Mendel (*a*) (1914) present convincing evidence that cod liver oil, like butter fat and egg yolk fat, contains a large amount of fat-soluble vitamin, a substance of unknown chemical nature, which is essential for the normal growth and development of rats. Schabad (*a*) (*b*) (1910) showed that cod liver oil, per se, increases calcium retention in rickets. He

also found that phosphorus given with the cod liver oil materially enhances the latter in this respect. In tetany there is a gradual reduction of electrical irritability with a simultaneous increase in calcium retention. Brown, MacLachlan and Simpson (1920) confirm the findings of Schabad in tetany, and are convinced that the two diseases are intimately associated, in that all of their cases of tetany showed varying degrees of rickets. Howland and Park (1920) have conclusively demonstrated the effectiveness of cod liver oil as a therapeutic agent in rickets. They have shown that a definite correlation exists between the Röentgen-ray signs and the actual pathological condition. Calcium deposits in the cartilage cast well defined shadows. In animal experiments an increased calcium deposit can be demonstrated two days after the administration of cod liver oil. In human beings the calcium deposit in the cartilage is definitely demonstrable at the end of three weeks after beginning the administration of cod liver oil.

The above experiments are in harmony with the long accepted conclusion of many clinicians that this oil is more than a food and contains something which exercises a stimulating and alterative influence on the processes of assimilation and nutrition, thereby promoting normal metabolism and the production of healthy tissue. What is it in cod liver oil that causes the increased calcium retention in rickets and tetany? The question is open. Hess and Unger (1920) emphasize that rickets frequently develops in infants receiving too much milk, rich in fat, protein, and salts. They state that the fat soluble vitamin is not the controlling influence; that infants develop rickets while receiving a full amount of this principle, and that they do not manifest signs, although deprived of this vitamin for many months, at the most vulnerable period of their life.

Cod liver oil undoubtedly contains other substances which may account for its special properties. Iscovesco (1914) described a lecithid which he isolated from cod liver oil and later from beef heart, which apparently promotes the growth of rabbits and stimulates the development of the lungs. It is possible that a chemical substance closely associated with a phosphatid contained in cod liver oil, such as Iscovesco describes, may account for the increased calcium retention in rickets and tetany.

Liver Extracts.—In general, saline extracts of liver given intravenously, not unlike extracts of other parenchymatous organs, stimulate plain muscle tissue, depress the circulation, and may cause a fatal shock-like reaction. Voegtlin and Bernheim (*b*) (1910-11) state that 5 c.c. of a saline extract of dogs liver cause a considerable fall in blood pressure and other symptoms found in anaphylactic shock, such as muscular weakness, nervous depression, defecation and urination. Parker (1918) found that the saline extracts of the livers from rabbits, previously inoculated with cultures of bacillus typhosus and bacillus prodigiosus, are more toxic than the extracts of normal livers when injected intravenously into normal rabbits. Rogers and his co-workers (1915-16) are convinced that only the

residue, or the non-coagulable portion of an aqueous extract of liver, thymus, pancreas, and thyroid contains an active substance which depresses the circulation when administered intravenously. When injected subcutaneously, even in enormous doses, the extracts show no vasodilating effect. The liver extract, when injected subcutaneously, stimulates the gastric secretion and motility, and also promotes a vigorous flow of pancreatic juice. They conclude that the residue or non-coagulable portion of an aqueous extract of the various organs studied, contains practically all the material which can directly and immediately affect, through the circulation, the functional activity of any other organ. Stern and Rothlin (1919) state that the liver contains two different water soluble substances, one of which produces hypertonicity and the other hypotonicity of smooth muscle tissue.

The experiments of Walton (1914) indicate that saline liver extract inhibits the growth of adult mammalian cells in vitro.

Voegtlin and Myers (1919) have shown that an alcoholic extract of the mucosa of the duodenum, liver, heart muscle, and milk, after being submitted to a modified Funk procedure for the purification of vitamin, and introduced intravenously into dogs, contains a substance which depresses the circulation and stimulates pancreatic secretion and temporarily increases the flow of bile. Further experiments by Myers and Voegtlin (1920) indicate that the substance directly responsible for the stimulating action on the pancreatic secretion and bile flow, and the fall in blood pressure, may possibly be histamin, or a histamin-like substance. Histamin, according to Abel and Kubota (1919), is a widely distributed constituent of all animal tissues and organ extracts.

Conclusions

The Place of the Liver in the Endocrin Congeries.—From the foregoing data it appears that the liver plays an important rôle in the production of numerous internal secretions, in the broad sense of the term. That it may also contribute one or more true hormones is believed by some and this possibility cannot be denied. Convincing evidence, however, that such is the case remains yet to be offered.

SECTION XI

The Internal Secretion of the Pancreas and Its Disorders

The Anatomy, Embryology, Comparative Anatomy, and Histology of the Island of Langerhans. . . *E. V. Cowdry*

Anatomy—Morphology, Technical Methods of Investigation, and Relations—Blood Supply—Innervation—Embryology—Origin and Development—Comparative Anatomy—Histology—Histologic Morphology—Dytology—Reactions to Experimental Conditions—Relation to Diabetes—Secretory Phenomena. [From the Anatomical Laboratory, Peking Union Medical College.]

The Anatomy, Embryology, Comparative Anatomy, and Histology of the Islands of Langerhans

E. V. COWDRY

NEW YORK

Anatomy

Morphology, Technical Methods of Investigation, and Relations.—The islands of Langerhans are epithelial structures of very small or, often, of microscopic size, scattered throughout the pancreas.

Unfortunately we know comparatively little of their relations in man, though Bensley has devised methods of supravital staining which have greatly extended our knowledge of them in the guinea pig. Up to the present time these methods have not been applied in detail to other laboratory animals, and, since the dyes must be injected immediately after death into the blood vessels supplying the pancreas, it is doubtful whether they will ever be used extensively in man. Clark alone has attempted to do so and has shown that the condition in man approximates closely to that found by Bensley in the guinea pig.

In the guinea pig the islands of Langerhans can best be studied in a pancreas which has been supravitally treated by the injection, through the aorta, of a dilute solution of neutral red in physiological saline solution, for in this way they become specifically stained a dark red color. Such a preparation is illustrated in Fig. 1.

In size they vary from single cells to clusters of three or four, and to masses of several hundred. Sometimes they may be as much as one millimeter in diameter, though they are usually considerably smaller. In shape they exhibit great variability, rounded masses predominating.

By staining with neutral red, the islands may easily be counted and the errors introduced through the laborious study of serial sections avoided. For convenience of description it is customary to divide the pancreas into three parts, splenic, body, and duodenal portions. Bensley has found that the islands are relatively more numerous in the splenic portion, and Clark

has confirmed Opie's (*b*) observation that this condition obtains in man. In guinea pigs the average, as found by Bensley, is 22.28 islands per cubic millimeter. The entire gland contains in the guinea pig about 25,000 islands. These seem to be rather more abundant in young animals. There is considerable variation, even in animals of the same litter. The islands

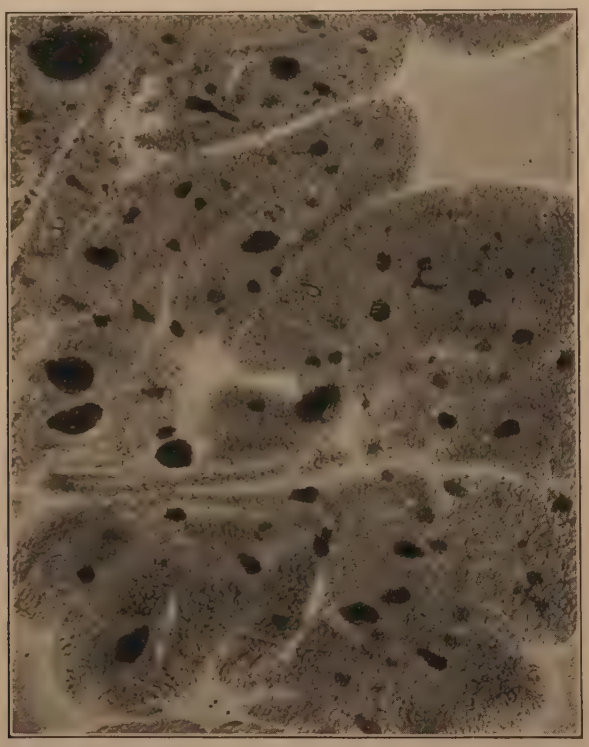

Fig. 1. Islands of Langerhans in the pancreas of the guinea pig stained by injecting neutral red into the blood vessels, after Bensley.

are usually larger and more abundant in the deeper parts of the lobule. Obviously, therefore, ordinary microscopic preparations cannot be relied upon to give us any idea of normal or abnormal variations in the number of the islands in the human pancreas.

Bensley has discovered in the guinea pig, and Clark has confirmed his observation in man, that the islands of Langerhans are connected with the ducts of the pancreas by a very delicate and intricate system of channels, which may be specifically counterstained by the addition of a little pyronin to the neutral red solution. These connections are shown in Fig. 2.

Blood Supply.—The blood supply of the islands differs sharply from that of the acinus tissue, for, as soon as the artery enters, it breaks up into a rich plexus of sinusoids, which permits the blood to come into very inti-

Fig. 2. Duct with system of delicate tubules connecting with the islands stained by injecting pyronin and neutral red into the blood vessels, after Bensley.

mate contact with the cells. Special information regarding the lymphatics is lacking.

Innervation.—Nerve fibers penetrate the islands in company with the blood vessels, but their exact mode of termination has not yet been definitely ascertained. We do not know whether they are secretory in nature.

Embryology

Origin and Development.—According to Pearce, the islands of Langerhans first make their appearance in human embryos of fifty-four millimeters, in which they are formed as outgrowths of the primitive gland tubules. At first they consist of solid clusters of a dozen or more cells each; they may be recognized by their pale staining nuclei and the affinity of their cytoplasm for acid stains, like eosin. He describes the penetration of blood vessels into these cell masses and their separation from the tubules through connective tissue formation. It seems, however, from the recent studies of Laguesse and Bensley, that the islands almost invariably retain their connections with the ducts. The cells finally become roughly arranged in columns and the island assumes its adult appearance. Slight but significant variations in rapidity in development in different forms are noted by Aron.

In the newborn guinea pig Bensley has found that, in addition to the well formed islands, there are myriads of single Langerhans cells incorporated in the epithelium of the acini. As development proceeds these iso-

lated cells become fewer and fewer, but a few persist, even in the oldest animals examined. On the whole, the islands seem to be rather more abundant in young animals. Throughout life there is a slow production of new islands from undifferentiated duct epithelium. The claims of certain investigators to the contrary, that island tissue is developed from the epithelium of the secreting acini no longer merit consideration.

Growth.—The comparative growth energy of the island tissue has not been measured by the inanition method. That is to say, we do not know whether the islands of Langerhans should be classified with those endocrin organs, like the parathyroids, which continue to grow in young animals held at maintenance of body weight by underfeeding.

Comparative Anatomy

Islands of Langerhans, or structures closely resembling them, occur in all vertebrates, from fishes to man, though they differ considerably in relative size and in number. It is interesting to note that in fishes the island tissue is condensed into a single large mass, quite unconnected with acinus tissue (Rennie), a condition which affords a unique opportunity for experimental study. Dewitt has investigated the arrangement of the islands in quite a comprehensive series of phylogenetic stages.

With the improved methods of enumeration at our disposal, we may confidently expect that studies on the relative amounts of island tissue in different forms will yield interesting results, because the varying demand for secretion may be correlated directly with some comparatively well known attribute of the organisms concerned. In this way it may be possible to secure a definite clue to the function of the islands.

Histology

Histologic Morphology.—The cells of the islands of Langerhans do not constitute a syncytium, as was formerly supposed. Their outlines are discrete and can easily be distinguished in suitable preparations. The cells are often arranged in cords with sinusoids taking the place of the regular ducts; for the lumina of the ductules, with which the islands are in contact, rarely penetrate into their interior. In the case of the larger islands, the cells are bound together by a very light connective tissue framework. In the smaller, on the other hand, it is quite common to find that the island cells are in direct continuity with the acinus tissue.

Cytology.—In ordinary preparations the cells of the islands all look alike (Fig. 3), but after special methods of fixation and staining, which we owe primarily to Bensley, it is possible to see that marked differences

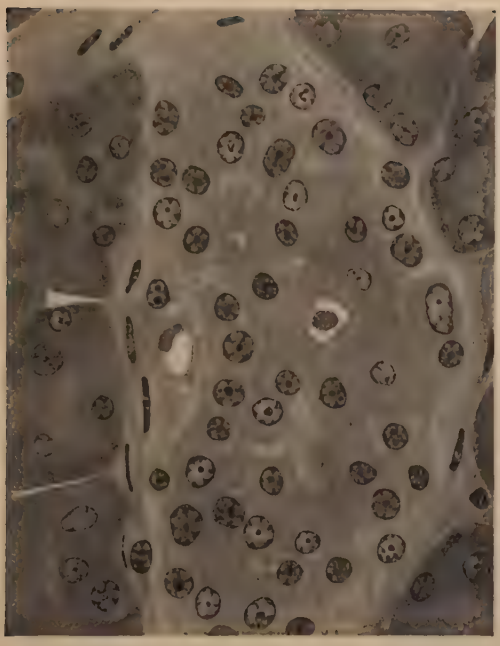

Fig. 3. Islet of Langerhans of a human pancreas fixed in Zenker's fluid and stained with hematoxylin and eosin, illustrating apparent similarity of islet cells (magnification 800).

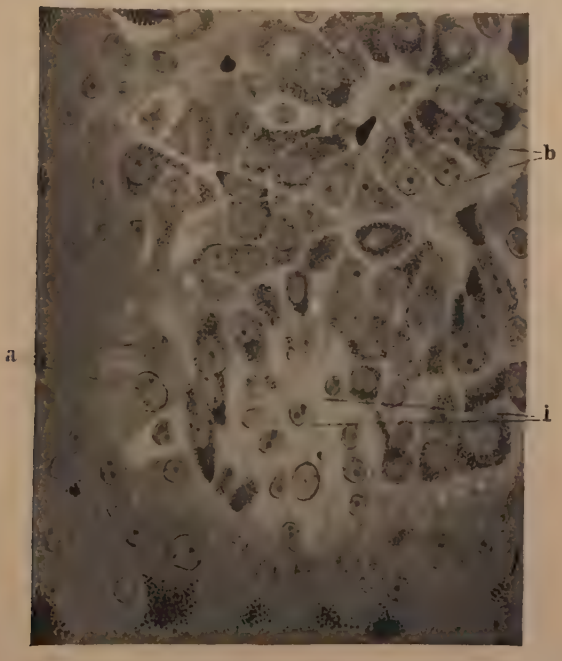

Fig. 4. Islet of Langerhans of a guinea pig's pancreas fixed in chrome-sublimate and stained with neutral gentian, after Bensley, revealing the true polymorphism of the cells: A cells (a), B cells (b), and indifferent cells (i) (magnification 800).

exist (Fig. 4). At least three different varieties may be distinguished in the guinea pig.

B Cells.—The B cells are by far the most abundant and constitute the bulk of the tissue (Fig. 4). They contain a large number of tiny granules, closely packed together, which, after fixation in the acetic-osmic-bichromate mixture, are basophilic, staining with methyl green. They also stain blue with neutral gentian, contrasting sharply with purple zymogen granules. Mitochondria occur, scattered throughout the cytoplasm, and sometimes show a tendency to be heaped up in the region of the cell adjacent to the sinusoid. The reticular apparatus is usually confined to the opposite pole of the cell, remote from the sinsoid, indicating the possibility of the existence of some measure of secretory polarity. The nuclei are roughly spherical and highly chromatic. Mitotic figures are never seen. Since the B cells are the only ones which it has been possible to alter in structure experimentally, we naturally suspect that they are responsible for the physiologic activity of the islands.

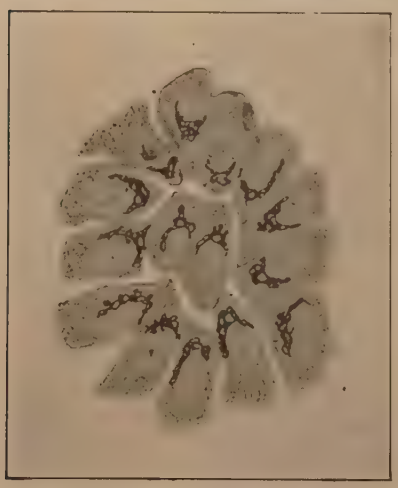

Fig. 5. Island of Langerhans in the pancreas prepared by Cajal's Uranium Nitrate Silver method which blackens the reticular apparatus. After Cajal.

A Cells.—The A cells are much fewer in number, to the point of being entirely absent in some islands, and they contain quite different granules, which stain with fuchsin, instead of with methyl green, after acetic-osmic-bichromate fixation. These cells may also be identified in neutral gentian preparations, owing to the fact that they are colored somewhat diffusely (Fig. 4). The solubilities of the granules are likewise distinctive. The reticular apparatus is much the same, but the nuclei are oval and comparatively poor in chromatin. Mitotic figures are absent and there is every reason to believe that these cells are as highly differentiated as are the B cells.

Indifferent Cells.—The "indifferent" cells are the rarest (Fig. 4). They are devoid of specific granulations, and appear quite clear in the sections. Only the reticular apparatus and the mitochondria, in addition to their nuclei, can be distinguished. They are apparently identical with the cells of the ductules, which may often be seen dividing. According to Bensley, we may regard them as the parent tissue, from which the A and B cells arise.

These three cell types are fundamental, since they occur in man,

several laboratory mammals, and in the toad. It would be well worth while to study their occurrence throughout the vertebrate scale, for qualitative studies in phylogeny are just as much needed as are the quantitative.

Reactions to Experimental Conditions.—The islands of Langerhans have proved thus far to be rather unresponsive to experimentation. Bensley, contrary to earlier observers, has found no noticeable change in number following secretin administration and acute inanition. The effect, if any, of chronic inanition still remains to be determined. Thyroidectomy is said to produce an increase in amount of island tissue. Kojima claims to have discovered that feeding rats with the posterior lobe of the hypophysis causes the cells of the islands of Langerhans to stain more intensely with Mallory's stain, on account of the accumulation in them of granules possessing an affinity for Orange G.

Relation to Diabetes.—Homans (*b*) alone has been able to correlate structural changes in the cells with apparent variations in physiological activity. He produced various degrees of diabetes in the dog by removal of portions of the pancreas, with the result that the mitochondria in the B cells became first accentuated and ultimately disappeared in association with hydropic degeneration, while those in the other cells showed no changes whatsoever. He believes that the B cells pour out a secretion which facilitates the metabolism of carbohydrates, and that these changes are indicative of initial hyperactivity followed by fatigue and exhaustion; and indeed this would seem to be the most likely interpretation. It is possible, however, that the alterations may result from the diabetes, or in other words, that the B cells are merely peculiarly sensitive to the altered conditions.

Secretory Phenomena.—Intracellular secretion antecedents are unknown. The mitochondria in Homan's experiments merely serve as indicators of the activity of the cells. There is no reason to suppose that they themselves produce the secretion. Thus far attempts independently to influence the specific granulations experimentally have proved unsuccessful. In the absence of further microchemical studies, we can only say that these granules are rather dense aggregates of cytoplasmic material necessary to the organization of the cell, and that they display a surprising constancy in phylogeny.

Pathology and Etiology . . . . . *A. S. Warthin*

Evolution of the Endocrinal Conception of the Pancreas—Relation of Pancreas with Other Endocrin Organs—Theories of Diabetes—Etiology of Disturbances of Pancreatic Endocrinal Secretion—Conclusion.

The Pancreas as an Endocrin Gland

Pathology and Etiology

A. S. WARTHIN

ANN ARBOR

The present position of the pancreas as an endocrin gland may be briefly stated:—*The islands of Langerhans constitute an endocrinal entity in that they regulate the body's use of the sugar formed from the food, and that disturbances of this function lead to diabetes.* This is the view accepted by the great majority of writers to-day. Its extreme representation may be found in the pronouncements of Allen: "It is necessary to keep clear the definition of diabetes as a deficiency of the internal secretion of the islands of Langerhans." "There is no diabetes with a normal pancreas." "Diabetes is synonymous with pancreatic disease."

This conception of the islands of Langerhans as endocrin organs is supported by certain essential and undisputed facts:—

1. The experimental removal of the entire pancreas leads to a fatal diabetes.

2. The removal of portions of the pancreas, as little as one-fourth or one-third, but not exceeding seven-eighths of its mass, leads to varying degrees of a tendency to the development of hyperglycemia and glycosuria when glucose is given by the stomach or subcutaneously. An animal may be brought so near to diabetes that this condition may be precipitated by the removal of as little as 0.1 gm. additional tissue. A subsequent contraction or degeneration of the remaining portion may also give rise to diabetes.

3. In totally depancreatized animals the occurrence of diabetes may be prevented by the transplantation into such animals of portions of pancreatic tissue. Subsequent atrophy or degeneration of the transplant will also be followed by diabetes.

4. The destruction of the entire acinar portion of the pancreas with preservation of the islets, as may be brought about through closure of its ducts, produces no glycosuria.

5. In cases of human diabetes pathologic changes are found with great frequency in the pancreas and in the islands especially. Some investigators never fail to find changes in the latter that they consider degenerative.

All of these facts taken into account, together with an immense amount of experimental investigation on the metabolism of the depancreatized animal and on the human diabetic, support the viewpoint that the pancreas is a gland of double secretion, producing in its acini the pancreatic juice which passes through its ducts into the duodenum for intestinal digestion, and in its islands an internal secretion which controls an important part of the intermediary metabolism. As to the exact nature of this internal secretion nothing is known, and we also are still in the dark as to the mechanism of its action. It is assumed to be of the nature of a hormone or enzyme which controls (inhibits) the consumption of sugar by the body-cells, or controls the synthesis of glucose into glycogen. Diabetes could, therefore, result from a deficiency of the pancreatic endocrinal secretion, either as the result of a too rapid conversion of glycogen into glucose, or from a failure of the tissue-cells to oxidize glucose, or their inability to fix glycogen.

While the conception of diabetes as the result of a deficiency in the endocrinal activity of the islets of Langerhans is accepted by the great majority of writers on diabetes at the present time, there exists a minority that does not accept the dictum that there can be no diabetes with a normal pancreas. This view they regard as too one-sided, holding that the internal secretions of the adrenal medulla, the thyroid and probably of the hypophysis also take part in maintaining the balance of sugar-metabolism, while a central nervous regulation is furnished by the sugar-center of the medulla (Claude Bernard puncture). From such a point of view there are many theoretically possible causes of diabetes, a failure of the incretory pancreatic function being only one of them. This broader constitutional viewpoint, according to its adherents, receives support in that, in the most severe forms of human diabetes with a history of heredity or familial occurrence, changes in the pancreas and in the islands have not been noted by trained, competent observers. If this is true, and if further studies show cases without lesions of the islets, then it is evident that in explanation of such cases we must either assume that there is no primary pancreatic diabetes, or that there is a one-sided deficiency of the inhibiting factor, or a stimulation of the exciting, or a lability of the depots. The fact that pathologic changes have been found in diabetics in other endocrin organs, thyroid and hypophysis, gives support also to the theory of a pluriendocrinopathic etiology of diabetes.

A neurogenic theory in explanation of certain cases of diabetes remains also to be considered.

Evolution of the Endocrinal Conception of the Pancreas

The evidence presented by the literature may now be examined. The mass of this relating to diabetes has reached such a magnitude that it is impossible in an article, of necessity so limited as this one, to present it adequately, hence there shall be attempted only a survey of the evolution of the conception of the pancreas as an endocrin organ in a very condensed form, with statements of conclusions reached or of facts demonstrated without details of experimental methods or observations. This evolution has proceeded along the lines of anatomico-physiologic, pathologic and biochemic observation and experimental investigation; but these will be taken chronologically together rather than to consider these various lines of development separately.

Early Anatomico-physiologic Conceptions of the Pancreas.—The earlier anatomists and physiologists regarded the pancreas as not absolutely essential to life or to health. In 1682 Conrad Brunner removed large portions of the organ from dogs without noting any change in the condition of the animal. It was not until 1856 that further investigations were made in this direction, when Claude Bernard attempted unsuccessfully to remove the gland completely. He then attempted ligation of the ducts and to shut off the pancreatic juice by injecting oil into them. As a result he noted the presence of fat in the feces. Later investigators (Schiff) failed to confirm these results. Bérard and Colin, in 1858, also attempted the total extirpation of the pancreas. They failed to observe the disturbances of digestion noted by Bernard, but found on autopsy that small portions of the pancreas still remained, to which, however, they were not inclined to ascribe any functional activity of importance. Klebs and Munk, in 1869, experimented with the definite aim of establishing a relationship between the pancreas and diabetes mellitus, attempting both ligation of the ducts and extirpation of the organ. They found no sugar in the urine, but the animals lived so short a time that the urinary examinations were not systematically carried out. It is also uncertain as to how much of the pancreas remained behind. The experimenters concluded that the coincidence of pancreatic affections and diabetes in man could be referred to coincident lesions of the solar plexus. Schiff (1872) repeated the experiments of Bernard, injecting paraffin into the excretory ducts of the pancreas in the effort to produce a complete atrophy of the gland. The animals thus experimented upon showed no signs of digestive disturbance and appeared to be perfectly healthy. In 1883, Claudia Ulesko, according to Truhart, was the first to ascribe to the pancreas "an internal secretion of a gland within a gland." Antedating Laguesse by ten years and Minkowski by seven, Ulesko's thesis was buried in the Russian journal *Wratsch* and

so lost. Finkler, in 1886, was likewise unable to produce diabetes by removal of the pancreas. Senn, in 1888, made some attempts to remove the pancreas in dogs and cats, but made no examination of the urine. Martinotti, as late as 1888, stated that the experimental removal of the entire pancreas in dogs caused no disturbance either of digestion or of their general condition. His results were generally accepted at that time. In 1889, Lustig noted a transitory glycosuria and acetonuria after removal of the cœliac plexus.

Early Clinical Observations on Coincidence of Pancreatic Disease and Diabetes.—During this same period, however, various clinicians were making observations that inclined them to believe that there was some relation between disease of the pancreas and diabetes. As early as 1788 Cowley had observed the association of diabetes with pancreatic calculi and atrophy of the glandular portion of the organ. This is the oldest known case in which the association between diabetes and pancreatic disease was noted. The patient was a robust man of thirty-three years of age, who suffered from diabetes for six months before death. The autopsy showed many calculi in the pancreatic ducts; the glandular portion was scirrhous. Bright, in 1833, observed a case of diabetes in which there was a tumor in the head of the pancreas obstructing the ducts and causing a fatty atrophy. The case described by Chopart in 1855 is undoubtedly Cowley's case. Griesinger found the pancreas atrophic in one of five autopsies on diabetics. He believed it to have no significance whatever. Fles and Hartsen each described a case of diabetes mellitus with atrophy of the pancreas. Harley saw a case of diabetes in which there was an abscess in the head of the pancreas obstructing and dilating the duct of Wirsung. Von Recklinghausen noted calculi in the pancreatic ducts with dilatation of these and atrophy of the glandular tissue in two cases of diabetes. In a third case he noted fatty atrophy of the pancreas. According to Seegen, the pancreas in thirteen out of thirty diabetics examined at autopsy in Vienna was found to be very small, soft and anemic. Frerichs, in 1866, found the pancreas in a case of diabetes showing cystic dilatation of its ducts which were filled with products of secretion. In five cases out of nine coming to autopsy he saw atrophy or fatty degeneration of the pancreas. Popper, in 1868, called attention to the relationship of obesity to disease of the pancreas. Other clinicians and pathologists (Lloyd, Elliotson, Bouchardat, Munk and Klebs, Cantani, Seegen, Sylver, Harnack, Külz, Schaper and others) during the middle decades of the last century observed cases of diabetes in which pancreatic changes in the form of calculi in the ducts, atrophy of the gland, and fatty atrophy were noted at autopsy. The coincidence of pancreatic disease and diabetes seems, however, to have made little impression upon any of them except Bouchardat, who is usually quoted as having, in 1845-6, been the first to have definitely connected pancreatic disease with diabetes; but, after observa-

tions extending over thirty years, this writer came to a final conclusion that the cause of diabetes was to be found in an excessive sugar-forming diet and the formation in the stomach of an abnormal diastatic ferment. The suspicion of any causal relation between diabetes and pancreatic disease went no further during this period than the assumption of some change in the composition of the pancreatic juice which either acted abnormally upon the sugar-producing foods in the intestine, or after the absorption of this abnormal juice caused a disturbance in the carbohydrate metabolism in the body tissues (enterogenous diabetes). Opposed to these views was that of Klebs who explained the coincidence of pancreatic disease and diabetes as dependent upon lesions involving the cœliac plexus.

The status of the pancreas, as regards its part in sugar metabolism and in the causation of diabetes, in the year 1876, is summed up in Senator's article in the von Ziemssen Handbook, Vol. XVI, as follows: "The behavior of the pancreas (in diabetes) is in the highest degree remarkable. This organ, which under other circumstances is in general so rarely the seat of morbid changes, at least of the grosser sort, is found diseased with surprising frequency, in particular either simply atrophied or, in addition, degenerated. Sometimes the degeneration consists merely in primary fatty destruction of the gland-cells, and sometimes it is induced by cancer, by the formation of calculi, and by obstruction of the efferent ducts, with cystic dilatation of the body of the gland. In certain cases the wasting of the gland has reached the highest degree, so that scarcely any discernible remnant of the secreting parenchyma was to be found. The frequency of these affections was not noted until somewhat recently, in consequence of Bouchardat's contributions." Senator then proceeds to a brief survey of the reported cases of coincident morbid pancreatic changes and diabetes, and then concludes: "It cannot be, then, that there is but an accidental coincidence; but a deeper connection must exist, and Klebs's view seems best founded, that the coexistence of diabetes mellitus and diseases of the pancreas depends upon lesions of the cœliac plexus. Either the disease (cancer, formation of calculus, and inflammation of the surrounding tissue) starts from the pancreas, encroaches upon the plexus, and gives rise to diabetes by destroying its ganglia, or else the cœliac plexus is first affected and in consequence thereof circulatory changes arise in the territory supplied by the cœliac artery, which lead to degeneration and atrophy of the pancreas."

During the next year, however, Lancereaux reported two cases of diabetes associated with severe lesions of the pancreas, fatty atrophy in one case, and atrophy with calculi and dilatation of the duct in the other. He believed that a causal relation existed between severe lesions of the pancreas and severe forms of diabetes characterized by rapid course with emaciation, etc. He explained the relationship as the result of the disturbance in the intestinal secretion of the gland. Lapierre, Baumler, and

others noted also the relationship between pancreatic changes and diabetes without advancing the solution of the problem. In his work on diabetes published in 1884, Frerichs states that atrophy, fatty infiltration and indurative conditions of the pancreas have often been seen in diabetes, and mentions two cases of his own, one of carcinoma of the head of the pancreas with stenosis and dilatation of the pancreatic ducts, the other with calculus obstruction of the duct, cystic dilatation and atrophy of the entire gland. He concludes that the pancreas, as a gland, as shown by Haidenhain, Klebs and Munk, and others has no influence on the excretion of sugar through the kidneys; and that it is undecided whether morbid conditions of this gland or its neighboring tissues could stimulate the cœliac plexus and thereby cause diabetes, since experimental work upon the abdominal nerves has led to uncertain results.

Demonstration of the Sugar Function of the Pancreas.—In 1889-90 appeared the classical work of von Mering and Minkowski which laid the cornerstone for the future conception of the pancreas as an endocrin organ. Conquering the difficulties of the operation they succeeded in obtaining complete extirpation of the organ, finding that dogs so depancreatized developed without exception a true permanent diabetes mellitus, glucose appearing in the urine as early as 4 to 6 hours after the operation, but usually later, often on the next day, reaching its height during the first 24 to 48 hours, even to 5 to 11 per cent before the animal received any nourishment. Even in dogs starved for seven days, the sugar did not disappear from the urine; when abundant food was taken larger amounts of sugar were excreted in the urine. Other symptoms of diabetes, as in man, were present in the form of hunger, thirst, polyuria, rapid emaciation and loss of strength. The sugar of the blood was increased. Sooner or later, in certain cases, acetone, acetoacetic acid and oxybutyric acid appeared in the urine. The glycogen content of the organs was early reduced to very slight traces. The diabetes persisted until the death of the animals, none of them living longer than four weeks. At autopsy the complete absence of the pancreas was confirmed. Marked fatty change of the liver was, also, a constant finding. From these experiments the investigators considered the diabetes to be the direct result of the total extirpation of the pancreas. When only a portion of the organ was removed no diabetes resulted. Only when the remaining portion of the gland was removed did the animal become diabetic. Injury to the solar plexus was also excluded. Ligation of the ducts was not followed by diabetes. Von Mering and Minkowski regarded their experiments as proving absolutely that the cause of diabetes was not the result of the absence of the pancreatic juice in the intestine; and concluded that the total extirpation of the pancreas must cause a disturbance of the intermediary metabolism within the organism. Diabetes must be the result of the loss of a *specific, hitherto unknown, pancreatic function* which is necessary to the consumption of

sugar in the body. They considered two possibilities, either that the pancreas normally destroys some ferment or poison in the body, so that after the destruction of the gland this substance causes an elimination of the sugar, or that the destruction of sugar in the organism is a normal function of the pancreas. Although von Mering and Minkowski did not use the expression "internal secretion" which had been introduced by Claude Bernard, in 1855, with reference to the glycogenic function of the liver, there can be no doubt that such a function of the pancreas was in their minds.

In the latter part of the same year appeared the report of the investigations of de Dominicis who had likewise been successful in producing diabetes through removal of the pancreas. In 1891, this author raised the question of priority, but as von Mering and Minkowski's publication preceded his by six months, and their conclusions were so different from his, there can be no doubt that the honor of this epoch-making discovery belongs to them, although de Dominicis has not been given sufficient credit for his apparently independent discovery of the main fact of pancreas-diabetes.

During the next few years the work of von Mering and Minkowski was repeated and confirmed by many investigators (Lépine, Hédon, Gley, Thiroloix, Harley, Capparelli, Schabad, Sandmeyer, Càvazzani, Seelig, Aldehoff, etc.), their general results agreeing, with more or less variation as to details. A few workers, as did Rémond, failed to conquer the technical difficulties of the experiment, and, as a result, denied the connection of diabetes with the pancreas. Experimental proof multiplied until it was shown that, not only in dogs, but in cats, rabbits, swine, toads and frogs also, extirpation of the pancreas is followed by diabetes. In fowls, the removal of the organ leads to a hyperglycemia without a constant glycosuria, owing to the holding back of glucose by the kidneys. In 1892, Minkowski made a full and extremely clear report of the progress made by himself and other investigators since his first communication with von Mering in 1889. The new points gained were the extension of the experimental demonstration of pancreas-diabetes to other animals, the proof that partial extirpation of the pancreas gave rise also to a more or less pronounced glycosuria dependent upon the amount of the gland removed, and the very important demonstration that a fatal diabetes could be prevented by leaving portions of the organ in place, or by transplanting such pieces, either within the abdomen or subcutaneously, and that subsequent removal of the transplants was followed by diabetes. Further, it was shown by Minkowski that removal of the salivary glands, thyroid, duodenum or mesentery might lead to transitory glycosuria not in any way comparable to the effects produced by removal of the pancreas. He also showed that phloridzin diabetes had nothing in common with the pancreatic. He thus greatly strengthened the case for the pancreas

theory, and in summing up all of the evidence concluded that the *sugar function of the pancreas is a specific one peculiar to this organ alone, and that a deficiency of pancreatic secretion leads to a disturbance of the internal metabolism of the organism. The cause of diabetes is either a deficiency of a normal function which controls the use of sugar in the organism, or, as the result of the extirpation of the pancreas, there is a heaping-up in the organism of some abnormal substance, or a deficiency of a normal function of the pancreas to remove a ferment-like or toxic substance, the retention of which in the organism causes the elimination of sugar. He regarded as the much more plausible view, that the pancreas has a normal function concerned in the utilization of sugar and the loss of this function is the cause of diabetes. As to the essential nature of this function only hypotheses could be advanced.*

To Minkowski, then, belongs the chief, if not the entire honor of first proving conclusively that the pancreas is an endocrinal organ. This view he did not express in the endocrinal phraseology of to-day; he did not even use the term internal secretion, because such a theory of endocrin metabolism and its terminology had not yet come into existence. Although Claude Bernard had as early as 1855 used the expression "sécrétion interne" in describing the glycogenic function of the liver, it had not yet acquired any specific meaning. Minkowski's work went far towards giving it such a meaning. Lépine (1889-91), after the first papers of von Mering and Minkowski had appeared, confirmed the existence of pancreatic diabetes, and in explanation asserted that the pancreas furnished an *internal secretion, a ferment with glycolytic power,* passed from the pancreas into the blood, taken up by the leukocytes and acting as a sugar destroyer. Lépine strengthened his theory by demonstrating that the glycolytic power of the blood was diminished in experimental pancreatic diabetes as well as in human diabetes. Removal of the pancreas removed this glycolysin from the blood and caused diabetes. It was soon shown by Arthus, Kraus, Sansoni, Gaglio, Seegen, Colenbrander, Minkowski and others that Lépine's conclusions were not justified; his methods were questioned, his statement that the glycolysis in normal blood was greater than in diabetic blood could not be confirmed, and the glycolysis observed by him was regarded as probably due to postmortem alterations in the blood. Further, the ferment-content of the blood alone would not have sufficed for the normal destruction of sugar. Nevertheless, this work of Lépine's, misleading as it was, performed a distinct service in laying emphasis on the possibility of an internal secretion formed in the pancreas, and the minds of investigators henceforth began to be concerned with this phase of the problem of pancreatic function and diabetes. In his critical discussion of Lépine's work and conclusions, Minkowski concludes that the conception of a glycolytic ferment is not applicable to the explanation of diabetes,

but that it is probable that the pancreas in some way affects the organs that use sugar normally, by freeing affinities by which the sugar molecule can be stored up. He considers it also possible that the sugar normally circulates in some loosely bound combination not available for the oxidation processes, and it is the function of the pancreas to break up this combination and make possible the normal oxidation of the sugar. Nommès, in 1898, had in mind the occurrence in the blood of a glycolytic ferment which he called "glycolysin."

The importance of the discovery of pancreatic diabetes by von Mering and Minkowski stimulated the development of an extraordinary interest in the anatomy and physiology of this organ. The suggestion that the glycosuria resulted from the loss of some kind of a pancreatic function other than that of the intestinal function aroused at once great opposition, particularly from de Dominicis, who unfortunately, no doubt, suffered in obtaining credit for his own independent discovery of pancreatic diabetes because of his wrong interpretation of the facts. He fought vigorously Minkowski's view, and attributed the glycosuria following extirpation of the gland to an absorption of poisons arising in the intestines from food-materials imperfectly digested as the result of the absence of the pancreatic juice. He claimed to be able to produce glycosuria in normal dogs, through the injection of a fecal extract or duodenal contents from depancreatized dogs. The transplantation experiments of Minkowski, Hédon and Thiroloix showed the incorrectness of de Dominicis' view, although he refused to be convinced. The investigators mentioned drew a portion of the pancreas out of the peritoneal cavity and placed it beneath the skin of the anterior abdominal wall. The later removal of the remains of the gland did not produce a glycosuria; but when the grafted portion was then also removed severe diabetes followed. Inasmuch as the grafted portion of the gland was still attached to a stalk of mesentery containing blood-vessels and presumably nerves, this experiment was not absolutely convincing to those who opposed the theory of a separate internal secretion, particularly to those who ascribed the experimental glycosuria to an injury of the nervous system.

Experimental Ligation of Pancreatic Ducts.—During the next fifteen years the investigations as to the nature of the pancreatic function and the explanation of experimental diabetes fall into a number of distinct groups: The effects of ligation of the ducts and destruction of the acinous portions of the gland; the morphology and pathology of the islands of Langerhans; and anatomico-physiological experimental work of various kinds. Based upon these researches various theories were developed: The acinar-theory, the island-theory, the acino-insular theory, and the neurogenic theory of diabetes. The literature concerned with the pancreas and diabetes now becomes so bulky, and there are so many conflicting results and opposing views presented by it that a critical survey

of the whole is impossible. Only the actual achievements that have advanced our knowledge of pancreatic function and disease can be touched upon.

The older experiments of ligation or blocking with foreign material of the pancreatic ducts were concerned chiefly with the changes produced in intestinal digestion. Atrophy of the acinous portion without diabetes was noted; but the state of the islands under such conditions was first observed by Vassale (1891), who found them intact. His observations were confirmed by Schultze (1900), Ssobolew (1901), Sauerbeck (1904), De Witt (1906), Visentini (1908), Tiberti (1908), MacCallum (1909), Kirkbride (1912), and Kamimura (1917). These investigators all noted atrophy of the acini with preservation of the islands, and absence of permanent glycosuria after ligation of the ducts. MacCallum varied the ligation experiment by separating the caudal portion of the gland and ligating the duct draining this area. A mild transient glycosuria followed. Seven months later the atrophied portion was removed and examined microscopically. It appeared to consist almost entirely of ducts and nests of cells that he regarded as islets, but was not absolutely sure of their identity. Kirkbride repeated this experiment with the same results, and through the use of Lane's differential staining method for islet and acinar cells (Bensley's neutral gentian) was convinced that the remaining parenchymatous tissue was made up of islet cells. On the other hand, Minkowski (1900), Pende (1905), Lombroso (1905-1910), Zunz and Mayer (1906) and Pratt (1910) found changes in both islands and acini. The injection of oil into the ducts led to necrosis of both islands and acini. Kamimura's research is the last important one in this line (1917). He found that ligation of the pancreatic duct of the rabbit led constantly to a complete atrophy of the parenchyma, while the islands of Langerhans were spared. The animals remained in good condition. The production of an adrenal or hepatogenous hyperglycemia through injection of adrenalin or diuretin, or through intravenous injection of grape-sugar, produced the same variations in the blood-sugar as in normal animals. Kamimura concludes that the intact islands remaining after ligation-atrophy furnish the inner secretion of the organ which stabilizes the carbohydrate metabolism of the animal. In another research he found that injections of cytolytic sera obtained from islet tissue produced no glycosuria.

Island-theory of Internal Secretion.—The island-theory was independently suggested by Laguesse (1893); he considered the cells of the islets as possessing an internal secretion of importance in the carbohydrate metabolism, while the acinar parenchyma secreted the external digestive juice. He advanced a "balancement" theory of a progressive cyclic transformation of acini into islands and the reverse for the complete production of both secretions, basing this view upon apparent morphological transi-

tions between acini and islands. The view that the islands are not independent structures but develop from the acinar parenchyma, or that transition-forms exist between the two was held by many writers (Lewaschew, Schmidt, Herxheimer, Karakascheff, Marchand, Benda, Gutmann, Hertel, Koch, von Hansemann, Vincent, etc.; while among anatomists Diamare, Rennie, Massari, and De Witt have represented the "separate organ" view of the islands. Karakascheff regarded the islands as having no specific significance for diabetes, but interpreted them as undeveloped portions of the parenchyma, probably reserve organs. Von Hansemann strongly opposed the island view, and considered the islands to be variable pictures representing non-secreting portions of the parenchyma and that the pathologic changes found in them are without significance and in no way influence the pancreatic secretion. Herxheimer took a middle point of view, ascribing both an external and internal secretion to the pancreatic cells. He believed that the islands develop from the acini, losing their external secretion and taking on the internal function. Diabetes will be caused by the loss of function of either component, but more rapidly by a loss of that of the islands. This view was accepted by C. Koch, Lombroso, Fahr and others. Fahr (1914), on the ground of both experimental, clinical and pathologic studies, concluded that neither the parenchyma alone nor the islands alone regulated the sugar metabolism, and that the pancreas possesses other functions than that of sugar regulation.

Pathological Changes in Islands in Diabetes.—Although Ulesko and Laguesse had suggested that the islands of Langerhans might be concerned in the internal function of the pancreas, it was Schäfer (1895) who first advanced the hypothesis that pathologic alterations of these structures are responsible for diabetes. Schlesinger (1891), Dieckhoff (1894), Kasahara (1896) had noted pathological changes in the islands in both diabetic and non-diabetic cases. Both Dieckhoff and Kasahara regarded their findings as unfavorable to the island theory. Human diabetes offered abundant pathologic material for purposes of study, and in the early years of the new century there appeared the pathological observations of Opie, Ssobolew, Herzog, Weichselbaum and Stangl, Sauerbeck, etc., which gave a stronger impetus to the island theory. Opie studied thoroughly the pancreatic changes in five cases of diabetes; in three of these the cells of the islands showed a complete hyaline change, in the other two cases the same condition but less marked. The acinous parenchyma was more or less altered in all. In non-diabetic cases the hyaline change was not found. Opie's study (1901) did much to advance the island theory. In the next year Wright and Joslin reported the finding of the same hyaline change in three out of nine cases of diabetes. Ssobolew found changes in the islands in fourteen out of sixteen cases of diabetes, in the form of diminished number, complete absence, fatty degeneration, pyknosis, and vacuolation with chromatolysis. In cases of advanced

sclerosis of the pancreas without diabetes he also found marked changes in the islands. In a case of "nervous" diabetes he found a fatty degeneration of the islands; in 1904 in a case of traumatic diabetes he found a portion of the pancreas with altered islands, while other portions showed a new-formation of apparently normal but very large islands (vicarious hypertrophy). In 1907 he reported seventeen cases of primary pancreatic carcinoma without diabetes, and explained the absence of the latter as due to the preserved condition of the islands. In all of the reports of these findings he upheld the island theory. Hansemann (1901) attacked Opie's findings, finding a hyaline change of the islands in only six cases out of thirty-two of diabetes. He regarded it as a secondary change. In the majority of his own cases he found a granular atrophy or polysarcia which he also considered secondary. He opposed strongly the association of the islands with the internal function of the pancreas.

Weichselbaum and Stangl (1901) examined the pancreas in thirty-two cases of diabetes, and found in the majority of them, not the granular atrophy of Hansemann, but a simple atrophy of the islands with pale-staining cytoplasm, often deeply-staining contracted nuclei and an increased fat content. The pale-staining of the epithelium of the islets has led others to interpret this as a "hydropic degeneration," although the writers themselves did not use this term. In some of the tubules they found pink-staining cells (centroacinar) which they thought might represent the hyaline change described by Opie. Opie's description of this as a hyaline degeneration of epithelial cells evidently threw them off the track, as they also describe islands resembling obliterated glomeruli in the kidney, undoubtedly the hyaline fibrosis of the islands recognized to-day as the most common change in the diabetic pancreas.

In five cases of diabetes Herzog found similar changes in the pancreas. The islands were diminished in size and number and surrounded by thick capsules. Hyaline degeneration, as described by Opie, occurred here and there in one case. In another case serial sections showed no trace of islands. In general the acinous tissue showed no marked changes, occasionally it was replaced by fat or connective tissue. Herxheimer found interacinar sclerosis in the pancreas in fourteen of twenty diabetics; six of these showed no changes in the islands, while in the other eight cases the islands were more or less altered. Two cases showed fatty infiltration and sclerosis of the entire gland; the remaining four showed no changes in either islands or acini. In what he took to be a large island he saw an excretory duct; also marked proliferation of the collecting ducts and transition forms from these to the island tissue. Basing his belief largely upon the statistics of Truhart (1904) that in only thirty-one cases out of five hundred and seventy-four diabetics was a hyaline degeneration of the islands found, Herxheimer denied the view expressed by Opie that this degeneration is the cause of diabetes. Schmidt found no changes in

either islands or acinous tissues in eight out of twenty-three diabetics. In fifteen other cases only two showed severe changes in both islands and acinous tissue. Of fourteen cases Gutmann found the pancreas perfectly normal in two. In other cases the acini or the whole pancreas was atrophic; in some of these the islands were few and showed thickened capsules, while in others they were numerous, hyperplastic and appeared to be connected with the acini in some places. Gentés, Fischer and Lépine saw cases with island changes.

Sauerbeck examined the pancreas of seventeen cases of diabetes and of sixty-four non-diabetics. These he included in an analysis of 176 cases of diabetes in which the pancreas had been examined. Fifteen showed no changes in islets or acini; thirty-two showed marked changes and twenty-five slight of both tissues. In nineteen cases the changes were more marked in the acini, in fifteen cases in the islands; in twenty-seven cases changes were found only in the acini, in six cases only in the islands. In the pancreas of non-diabetics precisely similar changes occurred in some cases, acini and islands might be either both markedly changed or entirely normal, or one or the other might be normal while the other showed lesions. In spite of this pathologic-anatomic evidence Sauerbeck favored the island theory on other grounds.

In the pancreas of fifteen cases of diabetes examined by Halász changes were found in both islands and acini. In eleven cases Karakascheff found more or less degeneration of the acinous parenchyma with preservation of the islets. By means of serial sections he was convinced that the islands proliferate and form acini. Through embryologic studies he also came to the conclusion that the islands were not definite organ-entities, but only early stages in the development of the acini. Gutmann and Herxheimer on the grounds of pathological investigations concluded that islands were developed from acini; on the other hand Schmidt, Lazarus, Reitman and others affirmed that the acini arose from proliferating collecting ducts.

Pathologic studies of the pancreas from cases of human diabetes were made also by Thoinot and Delamare, Lazarus, Dubs, Curtis and Gellé, Kausch, Miller, Lancereaux, Hoppe-Seyler, Carnot and Amet, Pende, Diamare, Visentini, MacCallum, Cecil, Koch, Saltykow, Fahr, Major, Heiberg, Gautier and Saloz, Winternitz, Labbé, Laignel-Lavastine and Vitry, Dubreuil and Anderodias, and Allen.

Diabetes has been many times observed in animals, but few studies of the pancreas in such cases have been made. Preller found interacinous pancreatitis with extensive degeneration of islands in a diabetic horse. Krumbhaar found in a diabetic dog marked hydropic degeneration and exhaustion of both Alpha and Beta cells with fibrosis of some of the islands.

The results obtained by these many pathological studies are widely divergent. The islands may be normal, they may be absent, atrophic,

hypertrophic, fibrous, sclerotic, hyaline, or show various degenerative changes of their epithelium, such as rarefaction, vacuolar or hydropic degeneration, fatty change, pyknosis, etc., or they may present a round cell infiltration. The comparisons of the pancreatic changes in diabetes with those found in the pancreas of non-diabetic cases show nothing specific for the former. Opie's hyaline change, once regarded by some writers as a specific change is only a fibrosis, a cicatrix, that is, an end result, and, of course, does not represent the primary lesion. Allen lays great stress upon the so-called "hydropic degeneration" as the essential primary lesion. There is, however, no positive proof that it is not a secondary one. Heiberg insists that the island changes are not qualitative, but are quantitative. Careful numerical estimates must be made of the number of the islets. The only absolute criterion is a deficiency of islets. Pathologically there are, according to Heiberg, two varieties of pancreatic diabetes, one in which the injury is confined to the islets, and another form in which both islets and glandular parenchyma are involved. These forms cannot be correlated with the clinical varieties. In the rapidly progressive cases, especially in the young, the changes are wholly confined to the islets. They may apparently be entirely absent.

In a diabetic of fifteen years of age, with rapid course, Gautier found no changes in pancreas or liver. The islets were normal. In some cases with a history of family incidence, no islets have been found after the most careful search. Ribbert, in 1915, holds that the islands in the cases of inherited diabetes are always few in number, while in the other forms regressive or inflammatory processes are predominant. It may well be that there is a congenital agenesia or aplasia of the islets, and such a malformation or developmental disturbance may explain the occurrence of congenital cases of diabetes. No doubt, there exist individuals whose tolerance to nutritive sugar is slight, and who throughout their entire lives are in danger of being thrown into a chronic disturbance of sugar tolerance through any one of countless slight injuries not harmful to the average individual; in other words, such individuals possess a sugar idiosyncrasy.

Winternitz has reported a case of diabetes extending over eighteen years, in which hyaline islets were present, with a new-formation of islets occurring more rapidly than their degeneration. He concludes that the pancreas is only one link in the chain controlling carbohydrate metabolism. Diabetes may occur when the pancreas is perfectly normal, as a result of lesions of the central nervous system or a disturbance in certain endocrinal glands. When the pancreas is involved the essential lesion is in the islands. Very recently Dubreuil and Anderodias have reported a most interesting observation in the case of a new-born child of a diabetic mother in which the islets were found markedly hypertrophic, 20 to 30

times the normal bulk. The authors explain this as a compensatory hypertrophy of the islets of the fetal pancreas to secrete more glycolytic ferment in order to preserve a normal glycemia of the fetus. They consider this an important proof of the regulating function of the islets with reference to the blood-sugar.

The results of the pathologic study of the changes in the pancreas resulting from animal experimentation are just as widely divergent as the autopsy findings in human diabetes. Ssobolew, Schultze, Sauerbeck, MacCallum, Kirkbride, etc., have reported preservation of the islets with atrophy and fibrosis of the acinar portion after ligation of the pancreatic ducts. Minkowski found that ligation of the duct in guinea-pigs caused a general fibrosis of both acini and islets. Pratt reported a similar destruction of both islands and ducts, and further affirms that all of the islands may disappear without the production of diabetes. Milne and Peters found that both islets and acini disappeared after ligation of the duct in rabbits and cats. In dogs they found that a very small portion of the gland left behind is sufficient to prevent diabetes; this portion becomes hypertrophic with very large acini, and in many cases the islets disappeared. Allen also saw some cases in which no islands were found, but in the majority of his cases the islands were intact.

The apparent contradictions regarding the significance of the pathologic conditions are undoubtedly due in part to a lack of a definite standard among pathologists and workers as to what is normal for the pancreas. Much of the trouble comes from different interpretations of the same histologic picture. Particularly is this the case with regard to the supposed transition forms between acini and islands, the regeneration of new islands, island hypertrophy, etc. The question of the new formation of islets is particularly difficult. The writer is convinced that the majority if not all of the formations interpreted as new islets are only regeneration forms of acini arising from duct proliferations. The whole question of the anatomic and functional independence of the islets is still unsettled. Many writers have regarded them as only functional stages of the acinar tissue. Dale, Vincent and Thompson believe that a new formation of islands from acinar tissue can be produced by injections of secretin. Bensley by means of vital staining and microchemical methods could not confirm this, but believes that the islands have staining properties quite distinct from those of the acini, an argument for their anatomic and functional independence. Homans confirmed Bensley as to the nonformation of islands under the prolonged stimulation with secretin and that the islands contain specific granules which allow of their positive identification. He holds that there is no evidence of the conversion of acinous tissue into islets or the reverse. On the other hand, Oertel believes that the normal histologic picture of the pancreas is a very variable one because of normal processes of progression and retrogression nor-

mally going on in the gland. Pathologic exaggerations of these processes may be found in the form of an essential atrophy of the organ.

The workers who have busied themselves with anatomico-pathologic changes in the pancreas in human and experimental diabetes may be classed as follows: Those who attribute the external secretion to the acini, and the internal secretion to the islands, and consider lesions of the latter to be the cause of diabetes; those who attribute to lesions of the acini the preponderating rôle in the genesis of diabetes; those who hold that the internal secretion of the pancreas belongs to both acini and islets, and that generalized lesions of the pancreas are by far the most common findings in human diabetes. Lombroso is one of the chief representatives of this group. The great majority of observers agree that the pancreas is an organ of internal secretion, (islets or acini alone, or both concerned) which takes part in the regulation of sugar metabolism. That this sugar-regulating function of the pancreas is not the only factor involved in the normal regulation of the carbohydrate metabolism, but is only a link in a complicated chain involved in this metabolism seems most probable from all of the evidence so far gained. Diabetes might, therefore, occur as a result of a disturbance in some other member of this chain while the internal function of the pancreas is normally produced. If it cannot now be affirmed beyond doubt that all cases of diabetes are due to pancreatic disease a certain number of them are definitely associated with alterations of this island.

Researches as to the Nature of the Internal Secretion of the Pancreas.—With the growing belief in the endocrinal function of the pancreas experimental investigations became more and more concerned with attempts to prove the existence and character of the hypothetical hormone. The researches began to follow physiologic or biochemic lines rather than anatomic.

Pflüger's idea of "duodenal diabetes" and of the nervous origin of diabetes, as opposed to the internal secretion theory, had first to be disposed of. This investigator maintained that the pancreatic diabetes of von Mering and Minkowski was really a duodenal diabetes, caused by the destruction of nerves passing from anti-diabetic centers in the wall of the duodenum. Ehrman, Lauwens, Rosenberg and Minkowski showed that the total removal of the duodenum in the dog did not cause diabetes; Pratt separated the pancreas from the duodenum without producing glycosuria; and Rosenberg showed that Pflüger's duodenal diabetes in frogs was a glycosuria due to exposure to cold, his frogs having been kept on ice. Martina freed a portion of the pancreas from its vessels and nerves and transplanted it into the spleen of a dog, which survived the extirpation of the remainder of the gland for three months in spite of the development of a well-marked diabetes. This gave a firmer position for the internal secretion theory as opposed to the neurogenic. Forschbach,

in 1909, discovered that the parabiosis of a depancreatized dog with a normal animal either prevented diabetes or reduced the glycosuria to one of a slight degree. From this it can be assumed that the normal dog furnishes some substance to the blood which, carried into the depancreatized dog enabled it to assimilate sugar.

In 1911, Carlson and Drennan found that glycosuria did not follow total pancreatectomy in a pregnant dog until after the fetus was removed. In 1913, Lafon confirmed this important discovery, and explained the prevention of diabetes in the mother before delivery as due to the passage of fetal pancreatic hormones into the maternal circulation supplying her deficiency. It is also possible that her sugar might be consumed by the placenta or the fetal tissues. The experiments of Carlson and Drennan, Forschbach and Lafon as such offer strong support to the hormone theory in general but do not bring us any nearer to a knowledge of the nature of the pancreatic function.

Likewise, the numerous experimental investigations along physiologic, metabolic and biochemic lines have brought us no nearer an explanation of the problem. Some of the more important contributions may be briefly mentioned here. Cohnheim's studies seemed at the time to offer an explanation of the long-sought for internal secretion of the pancreas. He found that a fresh extract of the pancreas does not destroy sugar, and that muscle juice has only slight action, but when the two are combined the mixture acquired marked glycolytic power. The pancreatic substance is not destroyed by heat, while the muscle ferment is. The former is supposed to activate the latter so that the muscle is able to cause the combustion of sugar. These studies were confirmed by numerous other writers, but later writers have thrown doubt on their value. Herter found that if the pancreas be painted directly with a solution of adrenalin a much greater degree of glycosuria is brought on than by subcutaneous intravenous injections of adrenalin. He explained this as due to the greater readiness with which the adrenalin is brought into contact with the pancreas. Loewi found that the introduction of adrenalin into the conjunctival sac of depancreatized dogs or diabetics is followed by a marked dilatation of the pupil. This suggests that the pancreas secretes a substance antagonistic to adrenalin. This phenomenon is known as the Loewi reaction, and has been confirmed by Biedl and Offer, Falta, Cords and Bittdorf, who obtained positive reactions in a certain proportion of cases of diabetes. Other workers have seen only negative results. Numerous investigators agree in holding the view that the sugar in pancreatic diabetes comes from protein metabolism and from the glycogen of the liver as long as this organ contains it, and is passed out of the body through the urine, because neither the muscles can use it nor the liver store it. Vahlen believed that he obtained a substance from the pancreas that produced the destruction of sugar in a purely katalytic

manner. De Meyer found that if the liver be perfused with Ringer's solution it lost less glycogen if pancreatic extract was added. When the liver of a depancreatized animal was used its function of storing glycogen could be restored by adding pancreatic extract to the perfusing fluid. Taylor found creatin constantly present in the urine of diabetics. This he interpreted as an expression of increased endogenous catabolism due to an inability on the part of the tissues to burn sugar, or to the non-formation of creatin into something else. The total amount of creatinin excreted was not abnormally increased, even on a rich flesh diet.

Drennan affirmed that the amount of sugar excreted by a depancreatized dog in 24 hours became lessened when blood from a normal animal was intravenously injected. On the other hand the feeding of raw pancreas or the giving of pancreatic preparations to diabetics has been universally without success. Zülzer, in 1907, had found that he could prevent the development of an adrenal diabetes by the injection of a pancreatic extract; and a year later reported that he had used this preparation with success in treating cases of human diabetes. In the hands of other workers (Forsbach, etc.) the injection of Zülzer's pancreatic hormone caused severe toxic symptoms, and it was considered probable that the temporary diminution of the glycosuria was due to this toxic action. Knowlton and Starling found that the sugar-consuming power of heart muscle is reduced to a minimum or disappears altogether in hearts taken from depancreatized dogs. The addition of a boiled extract of pancreas to the blood circulating through the heart of a diabetic animal restores to the latter the power of utilizing the glucose of the circulating blood. Maclean and Smedley confirmed these findings; while Macleod found that the addition of pancreatic extract to the blood causes no difference in the comparative rates of sugar utilization by the skeletal muscles of either normal or diabetic animals. No conclusions were drawn by him as to the heart muscle.

Paton regards the production of glycosuria after depancreatization as due to the too rapid mobilization of sugar, and a failure on the part of muscular tissues to use sugar. These results indicate that the pancreas produces an internal secretion or secretions which inhibit the mobilization of sugar and are antagonistic to the secretions of hypophysis, adrenals and thyroid, and hence facilitate the utilization of sugar by the muscles as a source of energy. The inhibition of sugar mobilization may be brought about by an action upon the terminations of the true sympathetic system in the liver. Nothing, however, is known as to the nature of the second process. Verzär affirms that in pancreatic diabetes there is a loss of power on the part of the body to burn sugar to carbonic acid. Hédon (1913) believes the cause of pancreatic diabetes to be the absence from the arterial blood of glycolytic pancreatic internal secretion of the nature of a glycolytic ferment. Clark states that when the pancreas is

perfused aseptically with Locke's solution containing physiologic concentrations of dextrose there is no alteration of the reducing properties of the perfused solution, but something seems to be added to it that brings about a utilization of the sugar by the living heart to an extent that does not occur with the heart alone. This substance shows some of the properties of an enzyme, and may be identical with the hypothetical internal secretion of the pancreas so necessary to sugar metabolism. The experimental evidence suggests that the substance or substances obtained by perfusing the pancreas may be concerned in the normal activity of the pancreas concerned with sugar metabolism.

Jacoby (1916) thinks that diabetes in addition to being a disturbance of metabolism is possibly also a sugar intoxication. True diabetic disturbances are due to the hyperglycemia, not only to the metabolic processes through which too much sugar is formed, nor to the loss of sugar-destroying function, but also to the toxic effects of the abnormally long circulation of sugar in the blood. Murlin and Kramer noted that the administration of alkali to totally and partially depancreatized dogs improved the oxidation of glucose. Later Murlin and Craver announced that the treatment of human diabetes with sodium carbonate resulted in distinct clinical improvement in several patients.

Schäfer (1916) regards as the most probable hypothesis the presence of a chalonic or inhibitory agent in the internal secretion of the pancreas which affects carbohydrate metabolism. Provisionally this substance may be called *insuline*. Whether this is of the nature of an enzyme or an antacoid cannot be definitely stated, although most probably the latter, in accordance with what is known of the other internal secretions.

Lombroso interprets the fact that the injection of sugar into a diabetic animal diminishes the glycosuria instead of increasing it, by the hypothesis that sugar stimulates the elaboration of glycolytic enzymes on the part of these organs with which the pancreas collaborates to regulate glycolysis. Murlin and Sweet found that dogs with a previous gastrectomy developed little or no glycosuria upon removal of the pancreas. In such a dog given artificial digestion the general nutrition remained good. In dogs depancreatized after gastrectomy the profound toxemia of a simple pancreatectomy does not occur. They suggest that the pancreatic hormone preserves the proper concentration of hydrogen ions in the tissues for combustion of glucose; it may, therefore, be a peculiarly adapted alkali produced by the islands of Langerhans.

Beifeld, Wheelon and Lovellete found that various pancreatic and salivary gland preparations cause a vascular depression which they explain as due to an augmented irritability of the vasoconstrictor centers. Epstein and Baehr state that after pancreatectomy there are marked changes in blood volume which must be considered in estimating accurately the variation in sugar and other constituents of the blood. After pan-

createctomy in cats the terminal increase in hyperglycemia is due to a diminution in the permeability of the kidneys. This probably explains the excessive rise in blood sugar prior to the development of coma. A double nephrectomy in depancreatized animals causes a rapidly progressive hyperglycemia which is largely due to the gradual mobilization of carbohydrates from the liver and muscles. Kennedy and Burge found that the extirpation of the pancreas decreases the catalase content of the liver by about 75 per cent, resulting in a decreased output of catalase into the blood and a lessened supply to the tissues. The decreased catalase content of the latter may account for the imperfect oxidation in diabetes. The pancreas may form an internal secretion which is carried to the liver and increases the formation of catalase in this organ. Sajous (1917) regards the splenopancreatic internal secretion as represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal. He considers the main function of this secretion to be the protection of the organism from the effects of the toxic derivatives of albuminoid bodies of endogenous or exogenous origin, including toxins.

Palmer says there is no difference in the amount of dextrose in normal or diabetic tissues due to variation in the manner of producing hyperglycemia, whether by mouth, subcutaneously, intravenously or intraperitoneally. The concentration of dextrose in tissues varies directly with the degree of hyperglycemia. Lépine (1918) states that the sugar contained in the blood after pancreatectomy disappears on warming less rapidly than that in the blood of a normal dog, all sources of error avoided. The stimulation of nerves to the pancreas has the effect of increasing glycolysis in the blood withdrawn later. Ligature of the duct also increases it as the result of the increased absorption of the internal secretion caused by the increased pressure in the small ducts. The greater part of the internal secretion passes into the lymphatics. He further holds that all tissues contain two distinct substances concerned in the utilization of sugar, one an intracellular enzyme decomposing the sugar molecule, the other a thermostabile substance that has the power of activating the former. This he regards as produced chiefly but not exclusively by the pancreas.

Auer and Kleiner found that the subcutaneous injection of morphin sulphate in dogs with a pancreatic deficiency causes a rise in glycemia four times as great as that produced in normal dogs. As such animals are in a prediabetic state this morphin test may become of value in detecting a lowered carbohydrate metabolism in the human subject.

Hoskins and Gunning state that after pancreatectomy in the dog the blood pressure remains either normal or somewhat depressed. Reactions to standard injections of adrenin are usually augmented, while those to

nicotine become variable. Their observations do not support the theory that the pancreas exerts a depressing influence upon the sympathetic nervous system. Meltzer and Kleiner conclude that the sugar production following the intraperitoneal injection of adrenalin is not of pancreatic origin but most probably the result of its action upon the celiac ganglia or adrenals. The greater production of sugar resulting from painting with adrenalin of the unisolated pancreas is due to the escape of a large part of the adrenalin into the peritoneal cavity.

De Corral states that electrical stimulation of the vagus below the cardiac branches and after destruction of the hepatic branches causes a diminution of blood-sugar. This diminution occurs so rapidly that it must be assumed that the internal secretion of the pancreas at least increases the consumption of sugar in the tissues or in the blood. This takes place in normal conditions or in hyperglycemia. After a resting period the blood-sugar rises again in some cases, in which as a result of the stimulation it is lower than normal.

In discussing the nature of pancreatic diabetes Knowlton and Starling say that it has been suggested that the normal function of the pancreas is to diminish excessive production of sugar, and that in the absence of its restraining influence excessive production and mobilization result. On the other hand the fact that carbohydrates are not utilized by the body when administered to animals in this condition has been interpreted as showing that the tissues have lost their normal power of assimilating and utilizing glucose. A third suggestion, though without much experimental support, is that the sugar of the blood must be built up into some other form before it can be used. Their own experiments would seem to show that the pancreas normally produces a hormone which circulates in the blood, and the presence of which is necessary to the assimilation and utilization of the sugar of the blood by the tissue cells.

McCoy follows Allen in his conception of the nature of diabetes as due to a failure of the internal secretion of the pancreas, or as more explicitly expressed by Pavy, that there is a shortage or deficiency in the number or quality of the sugar-amboceptors by means of which the dextrose of the blood is made available for oxidation in the tissues.

Ervine's experiments showed that a depancreatized animal after the development of the hyperglycemia and glycosuria still consumes glucose at the same rate as the normal animal. He concludes that the hyperglycemia and glycosuria are dependent upon the rate of synthesis of glucose into glycogen and not upon an interference with the normal rate of oxidation. He believes, therefore, that the internal secretion of the pancreas is an enzyme similar to that of the external secretion, but diverted into the portal blood for the rapid synthesis of glucose into glycogen. Failure of this action results in diabetes. The diabetic is one who fails to synthesize the absorbed glucose into glycogen rapidly enough to prevent hyper-

glycemia. The absence of glycogen in the tissues accounts for the associated pathologic changes of diabetes, such as fatty degeneration and acetonuria.

From all of the mass of experimental work sketched briefly above, it can be seen that as far as our knowledge of the nature of the internal secretion of the pancreas is concerned we have only conflicting hypotheses; and in this respect we are not much better off than Minkowski was in 1892 after confirming so brilliantly his experimental work on pancreatic diabetes and announcing his conclusion that the pancreas possesses an unknown internal secretion necessary to the intermediary metabolism, and that failure of this function leads to the production of diabetes. We come back to that original thesis as the cornerstone of our whole conception of the pancreas as an endocrin organ. That loss of the pancreatic function through the removal of the gland or through extensive alterations of its structure, of the islands especially, leads to diabetes we know with absolute certainty, but as to the character and mechanism of this function we have only a number of hypotheses to offer in explanation, some of which are wholly contradictory. We have acquired a certain number of apparent facts that, as yet, we can not correlate or interpret. The case stands thus: All of the evidence up to the present time indicates that *the pancreas is an endocrin gland in so far as its islets are concerned. These produce an internal secretion containing an inhibitory agent (hormone or enzyme) which affects carbohydrate metabolism.*

Relation of Pancreas with Other Endocrin Organs

Disturbances of the carbohydrate metabolism are caused in various other ways than by extirpation or disease of the pancreas. Hyperglycemia and glycosuria may be produced by Bernard's sugar-puncture of the medulla oblongata, by stimulation of the splanchnics, administration of thyroid extract, injection of adrenalin, or may be associated with disease of the hypophysis, thyroid, parathyroids and adrenals.

Lorand demonstrated the fact that extirpation of the thyroid tends to prevent or suppress the development of glycosuria in depancreatized animals. Zülzer saw glycosuria disappear after the ablation of the two adrenals. He found also that adrenalin glycosuria is prevented by pancreatic extract and even pancreatic juice. Frouin found that pancreatic diabetes in a dog diminished after the removal of one adrenal and two-thirds of the other. Sweet and Ellis found that complete removal of the glandular portion of the pancreas caused marked changes in the spleen and thyroid. Mann and Drips regarded the changes found in the pancreas after the removal of the adrenals to be only those due to changes in blood-pressure. They found

no evidence of any specific relation between the adrenals and pancreas. Crowe, Cushing and Homans studied the effects on the pancreas by the removal of the anterior lobe of the hypophysis but did not obtain any definite changes. Cushing stated in 1910 that pancreatectomy leads to changes in the posterior lobe of the pituitary. Sweet and Allen found the secretory activity of the pancreas to be increased after partial or complete removal of the pituitary. Fry found that in diabetes definite histological changes occur in the anterior lobe of the hypophysis in the form of adenomatous masses of eosinophile cells, with colloid invasion of the anterior lobe, and areas of cellular degeneration. In cases of acute pancreatitis and carcinoma of the pancreas no changes or very slight ones were found in the hypophysis. Eddy found that the water-soluble portion of the alcoholic extract of the pancreas contains a substance capable of inducing marked increase in growth (vitamine).

Pemberton and Sweet studied the relation of the internal secretions to pancreatic activity. They concluded that the inhibition of the pancreas by adrenalin and pituitary extract is independent of blood-pressure. The inhibition by extracts of pituitary and adrenal bodies occurs when the pancreas is stimulated by its normal excitant. Edmunds holds that adrenalin inhibition of the pancreas is due to the lessened blood content of the latter and is not specific. Bell experimented as to the effect on the pancreas of the partial removal of the anterior lobe of the pituitary, but obtained negative results. He concluded that alterations in the carbohydrate metabolism are not always directly attributable to primary pituitary, adrenal or pancreatic disease, since the activities in this direction are closely related, but that the adrenals and the pituitary may indirectly affect the functions of the pancreas and vice versa. Since glycosuria is so often associated with disease of the pituitary, pathological changes in this organ should be looked upon as possibly secondary to the pancreatic lesion only when pancreatic changes have also been found in diabetes. He further says that it is probable that the endocritic cells of the pancreas have no direct relation to the genital functions, although the influence of the pancreas on the general metabolism and possibly on the other endocritic organs of the individual may exert an indirect control. Schäfer says removal of the thyroid tends to prevent, and removal of the parathyroids, to facilitate both pancreatic and bulbar glycemia and glycosuria. Hewer found that the irradiation of the testes or ovaries caused an inconstant hypertrophy of the islets of Langerhans, but this work is not very conclusive.

The interrelations of the endocrin organs, particularly the thyroid, pancreas and adrenals, in connection with hyperglycemia and glycosuria have been especially emphasized by Eppinger, Falta and Rudinger. Schäfer thinks that, aside from the liver, which acts as the main storehouse for the carbohydrates, a number of organs are concerned in governing the

metabolism and mobilization of those bodies, all of these organs being mutually interdependent. The pancreas through its internal secretion may be regarded as holding the central position, and preserving the balance.

Allen regards the polyglandular theory of diabetes as a pure speculation, and holds that there is no proof that disturbed action of other organs can produce either functional or structural abnormalities in the pancreas and thus serve as a primary cause of diabetes. He holds tenaciously to the view that there is no diabetes without pancreatic disease, and that the essential specific pathologic lesion of diabetes is the vacuolar or "hydropic degeneration" of the cells of the islets originally described by Weichselbaum. He regards this change as an exhaustion phenomenon due to functional overstrain of an endocrin organ. It is, therefore, in the writer's opinion, an end result of the diabetes, and not a primary pathological change; and its presence cannot be taken as proof that the islands were primarily the seat of alterations that gave rise to diabetes. Allen says: "In human patients, the islands present are apparently stimulated to meet a demand beyond their capacity. Presumably the cells respond with an actual or attempted increase of secretory activity for a larger or shorter time while appearing morphologically normal." The primary cause of diabetes may then be sought elsewhere than in the pancreas, if Allen's interpretation is true, in the sympathetic nervous system, for instance.

Theories of Diabetes

Allen's latest statement (1921) of his view of pancreatic diabetes may be given briefly, as follows: The islets of Langerhans are concerned, not merely in the combustion of sugar or storage of glycogen, but also in the maintenance of general tissues or reserves. In some manner an increase in supply of fat or formation of adipose tissue imposes a burden on the island function, and the reduction of any kind of food or of the body weight reduces the demand upon this function. This would indicate that the island hormone has both a catabolic and an anabolic rôle. As the diabetic deficiency is so much more prominent with regard to the carbohydrates, it is possible that the island function is directly related to this alone, and that other foods are concerned through their influence upon the carbohydrate metabolism, although this is not yet settled. Whether this relationship is direct or indirect, the status of the pancreatic hormone in general metabolism and of the disturbances of the general metabolism in diabetes is sufficiently important that treatment must be directed to it. The islands may be damaged by functional overstrain and saved by limiting the dietary burden. No recognizable lesions are produced in the pancreas by fasting. Experiments show that, as far as strictly normal metabolism is concerned,

the pancreas has little if any margin of safety; but it is large with reference to diabetes. The point at which experimental diabetes begins is sharp and definite. An animal may be brought so close to the verge of diabetes that it is brought on by the removal of as little as 0.1 gm. of additional tissue; at this point a new histologic phenomenon, the hydropic degeneration of the islets shows itself. Active diabetes must first be present in order for the hydropic change to occur. Its significance in human diabetes is that the islands present in the pancreas are stimulated to meet a demand beyond their capacity.

Allen's position represents the extreme pancreas-theory of diabetes. To him diabetes is nothing but an overstrain or exhaustion of the endocrinal function of the islands of Langerhans. What pathologic factors lie back of, or are correlated with this functional overstrain he cannot say, and he has added nothing to our knowledge concerning the nature of this function. He discards, as being nothing less than a superstition, any theory of pluriendocrinopathies as concerned in the formal genesis of diabetes. His conception of the pathology of diabetes, as far as formal pathogenesis is concerned, begins only with the morphologic changes interpreted as indicating an overstrain or exhaustion, with the end-changes rather than the essential formal causes of this overstrain. After all, what Allen really says is that diabetes is a disease that shows itself through the pancreas rather than that it is a disease of the pancreas itself.

Newburgh and Marsh (1921), in opposition to Allen, have shown that with a high fat diet in diabetes glycosuria may be avoided, the blood-sugar lowered and acidosis be prevented. Woodyatt (1921) likewise regards diabetes as a limitation of the body's power to utilize glucose and that the rational treatment is to bring the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste, and to adjust the supply of fatty acids in relationship to the quantity of glucose to limits compatible with freedom from ketonuria.

The more recent writers in Europe, those of the last year, take a much broader view of the essential pathology of diabetes. W. Langdon Brown (1920) holds that diabetes is a sign of exaggerated metabolism, evoked through the sympathetic and the associated endocrin glands, which first shows itself in relation to the most abundant food material, but as it advances expresses itself in relation to all. He regards it as a mistake to look upon the disease merely as a disturbance of carbohydrate metabolism. The carbohydrates represent, however, about 70 per cent of an ordinary diet, and are the most easily mobilized of all the foodstuffs. When metabolism is but slightly impaired, it will be most likely to show itself in relation to carbohydrates. In one stage the ability to use sugar may be impaired, but the power of converting it into fat may remain. Hence glycosuria may be associated with obesity; or, as expressed by von Noorden, some cases of obesity are to be looked upon as latent glycosuria.

As the disease progresses further fat metabolism becomes impaired, and diacetic acid appears; still further and protein metabolism, and even that of organic salts becomes involved. Back of the phenomena of metabolic disturbances lie the sympathetic and the endocrin organs. The sympathetic mobilizes the sugar into the blood by means of the endocrin glands, for the purpose of defense, while the parasympathetic stores it in the tissues as a reserve; glycosuria may be of *organic origin with structural changes in the endocrin glands* leading to an overaction of adrenal, thyroid and pituitary, or to an underaction of the pancreas; or it may be of sympathetic origin, with no evidence of structural changes in any endocrin gland, but producing a functional overaction of thyroid, adrenal or pituitary or an underaction of the pancreas. It is apparently true that the glycosurias of endocrinal origin are usually recognizable by other evidences of that origin, while ordinary diabetes shows no other signs of endocrinal disease.

Eppinger and Falta hold that diabetes is not due to the disease of any one endocrin gland but to a loss of balance between them. It has been shown that the balance may be disturbed by disease of any one of them, and experimental proof of such a balance is not wanting. In a dog rendered diabetic by removal of sufficient pancreatic tissue, removal of the adrenals will greatly reduce the glycosuria; the further removal of the posterior lobe of the pituitary with the pars intermedia, followed by removal of the pancreas does not lead to glycosuria. The balance, which had been disturbed by the first operation, tends to recover as the result of the second. When there is no disease of any one endocrin gland the balance is upset through the sympathetic. Langdon Brown maintains that this must be the case, that it is the sympathetic which simultaneously stimulates the glands that lower carbohydrate metabolism and inhibits the one that increases it. Since ordinary diabetes shows no evidence of other endocrin disease, and since glycosuria of thyroid or pituitary origin shows other symptoms of endocrinal disease, it is possible that the cause of pancreatic insufficiency is to be found in the sympathetic system. Of the pathology of the sympathetic nervous system we know practically nothing. Further, we know very little of the pathological conditions of the other endocrin organs in diabetes.

Kraus (1920) found in twelve out of twenty-three cases of diabetes, ten of these of ages varying from 14–41 years, the other two older individuals, constant and characteristic changes in the hypophysis, in the form of atrophy of the anterior lobe, changes in number (reduction), size and form of the eosinophile cells, pyknosis, and degeneration of the eosinophile and chief cells. He regards the eosinophile-cell apparatus of the anterior lobe as the bearer of a sugar-regulating function. Increase of the eosinophile cells leads to hyperfunction and lowers the carbohydrate tolerance, diminution of these raises the tolerance. The diminution of the eosinphile

cells in diabetes mellitus may be an expression of an automatic regulative diminution of function of these especial cells to relieve the insufficient islet apparatus. It is evident that the pathology of diabetes must be extended to a fuller comprehension of the changes in the endocrinal glands and in the sympathetic, and a much broader view than that of "pancreatic disease" be taken.

Herxheimer (1920) reviews the history of pancreatic diabetes, and concludes that, in opposition to Weichselbaum, Fischer, etc., he must reject the pure islet theory for the explanation of diabetes. He places himself on the side of Lombroso, Koch, Fahr, Fränkel, etc., who hold that the internal secretion of the pancreatic acini and that of the closely related islet epithelium are both concerned in carbohydrate metabolism. The latter, which has no connection with the external secretion, plays the chief rôle. All disturbances affecting both elements of the pancreas, particularly the islets, leading to a marked change in this hormone will cause diabetes. Herxheimer mentions the frequent occurrence of adenomas of the acinar tissue in diabetes, and interprets them as compensatory hyperplasias for the preservation of the internal secretion. The fact that hypertrophy and proliferation of the acinar tissue, leading to the formation of atypical lobules of acini, often adenomatous in character, are very frequently found in the diabetic pancreas gives color to these views. The writer has found them in all of his autopsy cases of diabetes in which there is a chronic pancreatitis. These formations are undoubtedly those so often interpreted as newly formed islands. In fact, the illustrations given by Opie and others of regenerated islands are nothing more than proliferations of the ducts leading to the new-formation of acinar tissue. Their general appearances often closely resemble superficially the appearances of an islet, but they all contain a lumen and develop centro-acinar cells, and arise from a proliferation of duct epithelium. That new islets develop is not yet positively shown; and the writer has never seen anything in pancreatic pathology to convince him that such a new-formation does occur.

Etiology of Disturbances of Pancreatic Endocrinal Secretion. Systematic pathologic studies of the pancreas show that morbid changes are of frequent occurrence in this organ. Atrophy, chronic interstitial inflammation, islet degeneration and fibrosis, regeneration and hypertrophic conditions of the acini, occur in varying degrees of severity in a large number of cases, both in diabetics and non-diabetics. The same pathologic lesions may exist under the two conditions; there is no qualitative specific pathology for diabetes; and a quantitative criterion, while holding for the great majority of diabetic cases, does not hold for all. In some non-diabetic cases the pancreatic changes, including those in the islands, are just as marked as in diabetic cases, while in some cases of diabetes there may be no apparent changes in the pancreas at all, or the

islets alone are greatly reduced in number. These cases are, however, the exceptional ones, and the writer has seen them only in young diabetics with a family history of diabetes. The great majority of cases of diabetes (in his experience all adult cases and a few young adults) present a chronic pancreatitis. Allen says it is present in every case, as a rule, with no exceptions yet demonstrated. The writer is convinced that the facts do not support this too dogmatic statement. In two cases of familial diabetes in young persons no trace of inflammation or sequelæ of inflammation could be found in the pancreas; the islets were entirely absent; the acini were hypertrophic but no regenerative formations resembling acini were found. As other writers have noted the same finding, a rule of "no diabetes without pancreatitis" is not justified by the pathologic facts. In twenty-four cases of diabetes studied by the writer a chronic pancreatitis was present in twenty-one of the cases; in two of the twenty-one cases the pancreatitis was associated with cholelithiasis and pancreatic lithiasis with chronic inflammation of the ducts. No evidences of syphilitic infection were found in the pancreas or in any other organ of these two cases. In the remaining nineteen cases histologic changes of syphilis were found in the heart, aorta, adrenals, testes, nervous system, as well as in the pancreas. Three only of the cases had a clinical history of syphilis, two of these were congenital infections, one was acquired, with a strongly positive Wassermann. In the remaining sixteen cases no clinical history of syphilis had been obtained. In two of these cases spirochetes were found in the myocardial and pancreatic infiltrations and in three others in the myocardium. The pancreatic lesion was the same in all of the nineteen cases, and was identical with the syphilitic lesions of the myocardium, aorta and other parts of the body. The writer is convinced that the pancreatitis is of syphilitic origin.

In 1916, with Miss Wilson, he reported six of the cases included in the total given above, calling attention to the important fact that syphilis is an etiologic factor in pancreatitis, and that if pancreatitis is a cause of diabetes, then syphilis must be reckoned with as a factor in the etiology of diabetes. This report attracted much attention, some opposition, but a surprisingly large amount of confirmation from clinicians as to the coincidence of syphilis and diabetes. In his "Harvey Lecture" for 1918 the writer presented a study of the pathologic conditions found in the bodies of 300 cases showing histologic evidences of syphilis. In every one of these cases inflammatory lesions of the syphilitic type, plasma cell and lymphocyte infiltrations were found in the pancreas, the changes varying from small scattered areas of fibrosis and infiltration to more diffuse processes involving large portions of the gland. (See Figs. 1-6.) The tail and body portions are especially involved in the syphilitic inflammations; while in the duct inflammations the head and body show the chief changes. In all of the more severe cases the islets show more or less

marked involvement. (See Figs. 7-9.) In some cases the hyaline fibrosis of the islands appeared to be as marked as in diabetic cases; and numerical

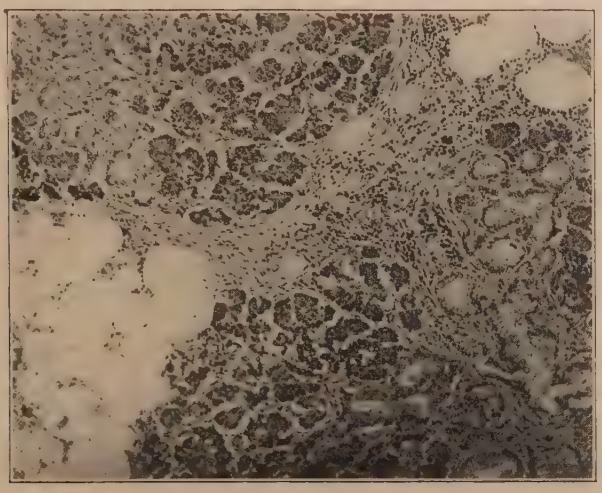

Fig. 1. Chronic syphilitic pancreatitis with diabetes. Spirochæta pallida was found in small colonies in the active areas of inflammation. Patient had no history of syphilis, no recognizable clinical signs and negative Wassermann.

estimations showed an apparent diminution in their number. The "hydropic degeneration" of Weichselbaum and Allen occurs in both diabetic and non-diabetic cases. Hypertrophic and regenerative proliferations of

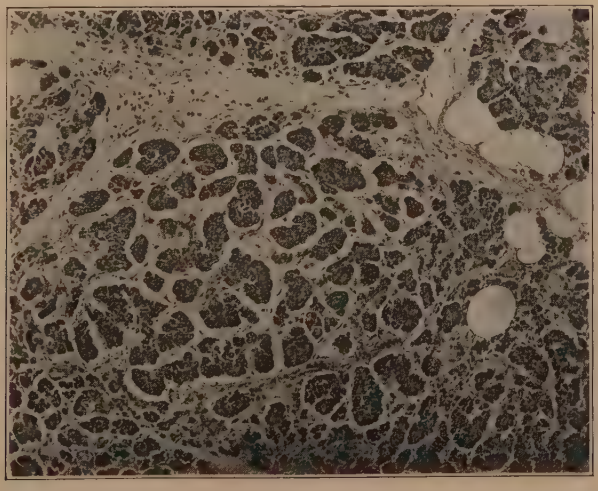

Fig. 2. Chronic syphilitic pancreatitis with diabetes. Spirochæta pallida found in heart and pancreas. No clinical signs of syphilis, Wassermann negative.

the acinar tissue are common in all of these cases, not infrequently to the extent of an adenomatous character. (See Figs. 10-12.) Many glandular formations superficially resembling hypertrophic or newly-formed islets

occur; none of these have the vascular relations of the islet, and they all appear to be acinar in structure. An interesting finding is the occasional

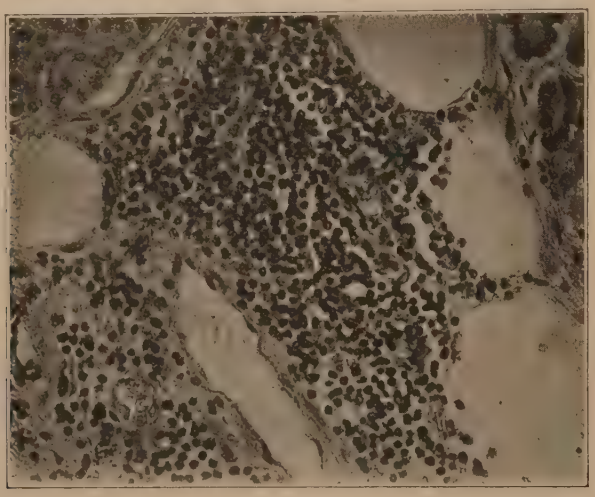

Fig. 3. Active area of plasma-cell infiltration in chronic syphilitic pancreatitis with diabetes.

occurrence of these new-formations of acinar tissue within the lumen of a larger duct.

The twenty-four cases of diabetes studied by the writer show, there-

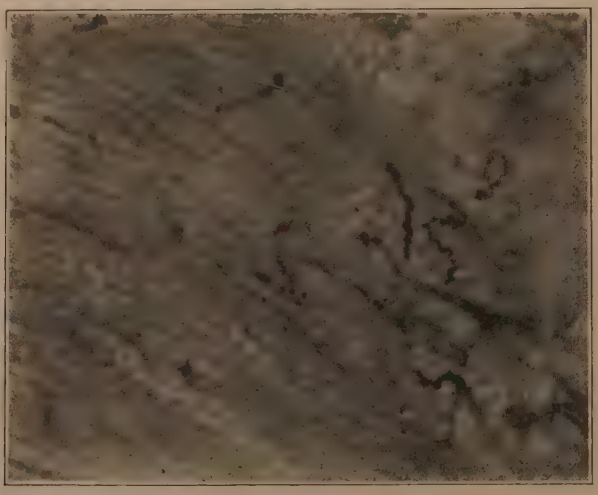

Fig. 4. Colony of Spirochæta pallida, in edematous, infiltrated interlobular connective tissue.

fore, three cases of agenesia or hypoplasia of the islets, probably congenital, two cases of chronic duct infection without syphilis, and nineteen cases of a chronic pancreatitis of a syphilitic nature. The study of the

pancreas in non-diabetic syphilities shows some degree of involvement of the pancreas in every case. The writer is, therefore, strongly of the opin-

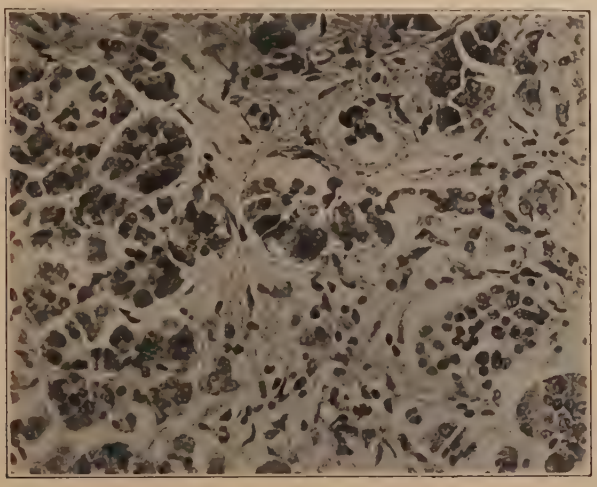

Fig. 5. Atrophy and degeneration of acinar tissue with fibrosis of stroma in chronic syphilitic pancreatitis with diabetes.

ion that latent syphilis is one of the most important causes of chronic pancreatitis, whether the latter is associated with diabetes or not. If pancreatitis is a cause of diabetes, it follows that syphilitic infection has an

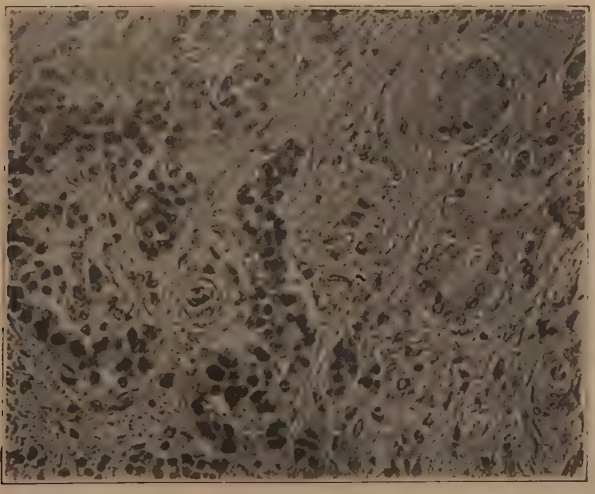

Fig. 6. Higher power view of acinar changes and interacinar fibrosis in chronic syphilitic pancreatitis. Healed, inactive area.

etiologic significance for this disease. On the other hand, if these chronic inflammatory changes in themselves primarily cause so much destruction of pancreatic tissue that a functional insufficiency manifests itself in the

form of diabetes it is surprising that this so relatively rarely occurs. It is, of course, possible that many cases of old syphilis are potential diabetics;

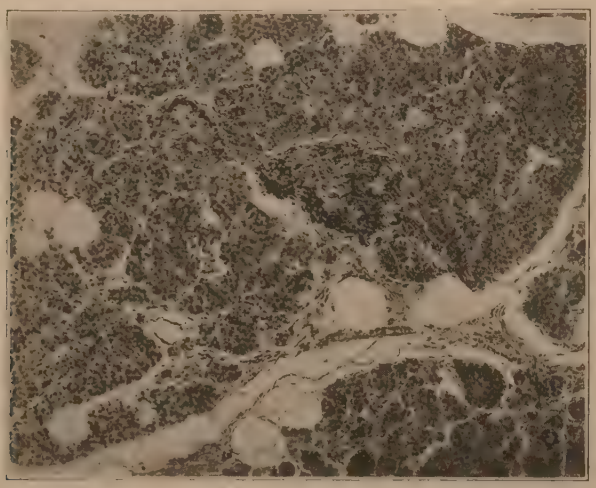

Fig. 7. Atrophy of acini, increase of stroma, fatty infiltration of stroma, hyaline fibrosis of islets with characteristic pyknotic hyperchromatic nuclei at periphery. Chronic syphilitic pancreatitis with diabetes.

and that any functional strain upon the pancreas may bring the functional weakness above the clinical horizon.

If pancreatitis is the essential pathology of pancreatic diabetes any

Fig. 8. Hyaline fibroid islet from chronic syphilitic pancreatitis associated with diabetes. Periphery of islet shows the hyperchromatic cells often mistaken for lymphocytes.

etiologic agent, infection, poisons, toxins, trauma, neoplasm, blocking of ducts, etc., that may injure the pancreas to such an extent that functional

insufficiency may be caused, becomes a cause of diabetes. The present tendency of many clinicians is to assign to general or focal infections an

Fig. 9. Large hyaline fibroid islet with hyperchromatic and pyknotic cells at periphery. The fibrosis is essentially a sclerosis of the capillaries of the islet.

important rôle in the production of pancreatic injury leading to diabetes, but this is only an assumption based upon general principles. The involvement of the pancreas in acute infections localized elsewhere, is very

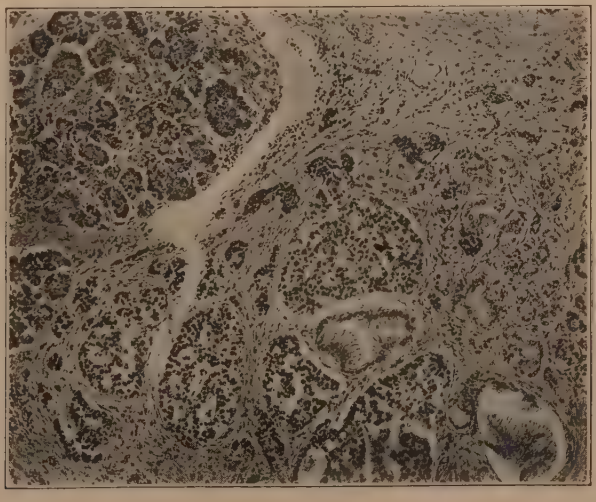

Fig. 10. New-formations of lobules in chronic syphilitic pancreatitis with diabetes. These arise directly from the epithelium of the ducts, develop collecting ducts, acinar lumen and centroacinar cells. Young forms of these are usually mistaken for new-formed islets.

rare, except as a terminal process. There is a possibility that mumps may cause such damage to the pancreas as to lead to diabetes, but proof

of this is slight. We know very little in fact of the pathologic processes in this organ, even less than we do of its normal endocrin function.

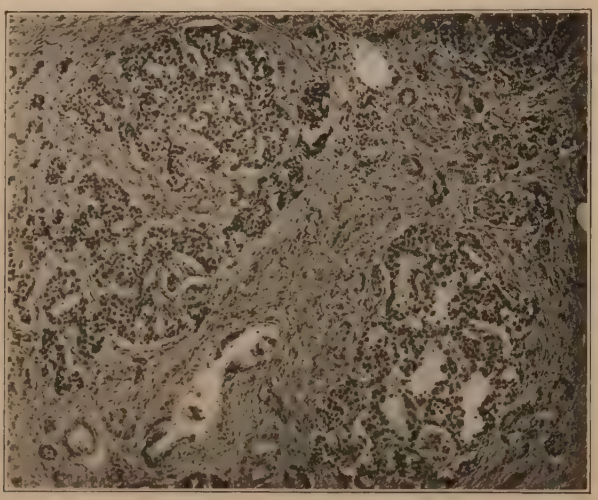

Fig. 11. Adenomatous new-formation of lobules of acinar tissue in chronic syphilitic pancreatitis with diabetes. Dilated acinar lumen.

It is very probable that, until the physiologic problems regarding this are solved, we cannot evaluate the pathologic changes occurring in the organ or apply them to an explanation of the functional disturbance. It

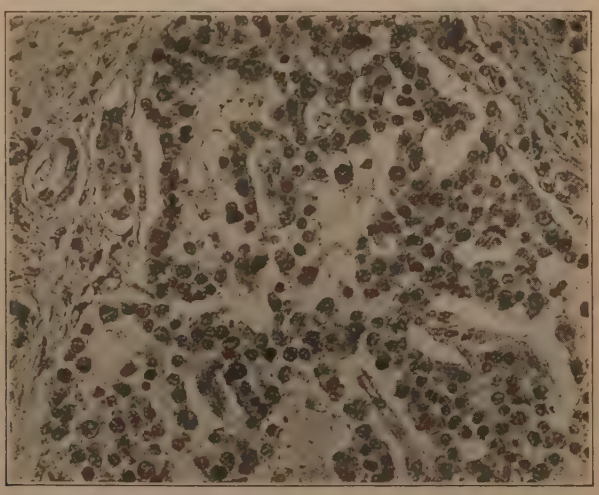

Fig. 12. High power view of new-formed acinar tissue seen in preceding figure. Dilated lumen with vacuolated cells and hyperchromatic nuclei.

must be constantly borne in mind that the islet changes seen at autopsy in the diabetic are an end-result. The hyaline islet tells us no more about the essential disturbance of the islet cells than do the hyaline glomeruli of the

kidney of the nature of the primary glomerular injury. Moreover, the hydropic or vacuolar degeneration of the islets upon which Allen lays so much stress as a positive diagnostic sign of diabetes is probably, as he himself recognizes, not an expression of diabetes itself but of cellular degeneration due to diabetes or is possibly glycogen or fat deposit. It is, in that case, of less diagnostic value in the pathologic diagnosis of diabetes than is the glycogenic vacuolation of the loops of Henle in the kidneys. This occurs only in association with glycosuria, but the islet degeneration is found when no glycosuria is present.

Heredity appears to be an important factor in certain cases. The familial occurrence of diabetes is well known. It may, in such diabetic families, be associated with other constitutional peculiarities, as the gouty or arthritic constitution, or with other endocrin-complexes (thyroid, pituitary). In many of these familial cases the pancreatic pathology is individual (agenesia or hypoplasia of the islands, absence of inflammatory changes).

Considering the broader conception of diabetes as an endocrinopathy, the etiology of the disease becomes more complicated and of greater possible variety. Lesions of the sympathetic, hypophysis, thyroids and adrenals, as well as of the pancreas, must be considered in the etiologic problem. Disturbances in any other member of the endocrinal complex concerned with carbohydrate metabolism may throw upon the pancreas a greater functional load leading ultimately to exhaustion, unstable histogenic equilibrium, lowering of resistance, and nutritive disturbances that ultimately express themselves in morphologic and chemicophysical changes of the islets, or of islets and parenchyma. Such a functional disturbance of the organ might even determine the occurrence of secondary or terminal infections of the pancreas, or increase its susceptibility to a generalized infection like syphilis.

Conclusion

That the pancreas is a gland of internal secretion is now universally accepted as a firmly established fact of physiology and pathology. Of the nature of this internal secretion we know nothing but that it is essential to the carbohydrate metabolism and is apparently of the nature of a hormone inhibiting the utilization of sugar; and is antagonistic to the secretion of the adrenal medulla, and influenced by the internal secretion of the thyroid and probably by that of the hypophysis, while its nervous regulation is furnished by the sugar-center of the medulla and the sympathetic system.

The majority of the writers on the pancreas regard the islets as the seat of this hormone production; a minority hold that both islets and acinar tissue are concerned in the production of an internal secretion.

Functional insufficiency of the pancreas in the production of this hormone leads to a disturbance of the carbohydrate metabolism, manifesting itself in varying degrees of a lessened sugar-tolerance, eventually diabetes. With this there may be associated disturbances in both fat and protein metabolism.

Pathological changes in the pancreas, particularly involving the islets, occur almost constantly in human diabetes, in the great majority of cases associated with a chronic pancreatitis. The relationship of these changes to the etiology of diabetes is not yet evident. The most common changes in the islands, regarded by many workers as specific in character, are most probably end-results and not primary lesions. The primary pathology of the functional inadequacy remains to be demonstrated.

If the pluriendocrinal theory of carbohydrate metabolism be accepted, the causes of diabetes must be varied. If the balance of this metabolism is kept by the pancreatic inhibiting hormone and the antagonistic adrenalin, influenced by the internal secretions of thyroid and hypophysis, and regulated by the sympathetic system, morbid conditions of any part of this endocrinal apparatus must give rise to disturbances of carbohydrate metabolism leading to glycosuria or diabetes. Disease of the pancreas seems, with our present knowledge, to play the chief rôle in producing such a metabolic disturbance. Back of the pancreatic changes there may well lie morbid conditions of other parts of the apparatus, particularly of the sympathetic system.

Leaving all hypotheses aside, the only reason for ascribing a special endocrin function to the pancreas is the occurrence of the metabolic phenomenon known as diabetes and the established relation between this condition and loss of pancreatic tissue. All that we know positively of the endocrin function of the pancreas is its highly specialized rôle in the utilization of glucose.

SECTION XII

The Salivary Glands, Stomach and Intestines as Endocrine Organs . . . . . *Fred C. Koch*

Introduction—Status of the Problem and Nature of Evidence—Endocrine Considerations of Various Digestive Organs—The Salivary Glands—Stomach—Intestinal Endocrine Function—Physiological Evidence as to the Presence of Secretin in the Blood and as to the Mode of Action of Secretin—Motilen or Peristaltic Hormone.

The Salivary Glands, Stomach and Intestines as Endocrine Organs

FRED C. KOCH

CHICAGO

Introduction

Status of the Problem and Nature of Evidence.—In this chapter the aim has been to give a critical review of the available published researches on this subject taken in its broadest sense. One does not have to go very far in his search for good physiological evidence before he is bewildered with the numerous conflicting reports, not only in the clinical phase of the subject, but particularly in the more scientific and experimental studies. The first desideratum is the actual evidence that certain or all of these organs do possess true endocrine functions. Unlike the main evidence obtained in such cases as the thyroid, suprarenal, parathyroid and pituitary, that is, the observed effects after removal of these glands, we here have been trying to establish endocrine functions more particularly upon the physiological effects resulting from the injections of various extracts prepared from the organs in question. When the effects produced have been more or less specific, as to nature and site of response, and particularly more or less quantitatively specific, as to origin of extract, then the evidence has been taken as indicative of a true hormone action. It is evident, of course, that unless the experimental data indicate a quantitative specificity, as to site of action and origin of extract, that the evidence is very unsatisfactory indeed. Even if the facts thus obtained are indicative in a positive direction, the evidence is by no means conclusive, in that the conditions existing during the experimental observations are by no means representative of normal physiological processes. It is a very different matter, on the one hand, to introduce into the blood stream substances which are obtained by the various extraction methods from an organ, and, on the other hand, to prove that the same substance or substances are really normally present in the blood flowing from the organ in question. The extraction method may produce substances entirely foreign to the blood stream. The other main line of experimental evidence which has been obtained is based on the transfusion or injection of blood where

the donor presumably contains a higher concentration of the active substance in its blood than the recipient, and then detecting this by a characteristic physiological response in the recipient. We shall learn that in neither case does the experimental evidence conclusively prove that any of the organs of the digestive tract act truly specifically as endocrine tissues. Nevertheless, it is conceivable that they may act thus, and even if they do not do so, such extracts, if properly prepared, purified and standardized, may be of considerable value clinically. It is, however, not likely that the clinical application will be along the lines of true organotherapy, that is, a substitution as in the case of the thyroid.

Endocrine Considerations of Various Digestive Organs

The Salivary Glands.—The first observations along these lines were made by J. C. Hemmeter (*a*) (*b*) in 1907-8. He concluded that in gastric fistula dogs, extirpation of all of the salivary glands causes a diminished gastric secretion and that this is equally true when the vagi are cut. In such animals he found a decrease in the rate of secretion, as well as in the activity of the gastric juice, but that this could be restored to the normal values by the intravenous injection of extracts prepared from dog's salivary glands, providing these glands were removed when it was known that they were functionally active. He could not bring about this stimulation by feeding food, previously chewed and mixed with saliva by other dogs, nor by feeding the salivary glands. He found lymph gland extracts inactive and the spleen slightly active. A. S. Loevenhardt and D. R. Hooker could not confirm the stimulating action of salivary gland extract on normal dogs. In reply to these findings, Hemmeter claims that one can hardly expect to be able to increase a normal secretion. Keeton and Koch (1915) also were not able to stimulate a resting stomach to secretory activity by submaxillary gland extracts, thus confirming the findings of Loevenhardt and Hooker. Swanson (1917), in studies on two dogs, before and after complete removal of the salivary glands, did not observe a decrease in the rate of secretion or of activity of the gastric juice, as measured by the Pawlow pouch. In fact, after the removal of the salivary glands a more strongly acid juice was obtained; this was very striking in one of the dogs. Hemmeter stands alone in both of his claims; that is, neither the lowered rate of secretion of a weaker juice as the result of removal of the glands, nor the stimulating effect of the salivary glands extract has been confirmed by others. The subject requires further investigation and at present the results do not indicate an endocrine function in the salivary glands. The only other suggestion of a salivary internal secretion is the work of Bruno Farroni, who reports that extracts of salivary glands have a marked glycolytic action on

glucose *in vitro,* and that, *in vivo,* such extracts to some extent inhibit morphin, phloridzin and adrenalin glycosuria. He suggests a possible functional relationship between the salivary glands and the pancreas.

Stomach.—*Early Work with Gastrin.*—In 1906 Edkins demonstrated in an anesthetized cat that the intraveneous injection of a 0.4 per cent hydrochloric acid extract of cardiac or pyloric gastric mucous membrane, causes a secretion of gastric juice, but that similarly prepared extracts from the fundus region do not possess this activity. The method he employed was that of washing out the stomach with water before and after the injection, and in case increased acidity was observed in the second washing, it was considered as proof of secretory activity as a result of the injection. This method is open to many objections, in that the anesthetized stomach is not a reliable criterion; also, in that the introduction of water alone may itself act as a stimulant to gastric secretion, and further, in that the intravenous injection causes only a slight and transient response in the gastric mechanism. Edkins interpreted his results as showing that a gastric secretin, *gastrin,* is elaborated in the pyloric region specifically. About the same time that Edkins made these observations, Gross (1906), independently, in Pawlow's laboratory, also came to similar conclusions. He found that the introduction of beef extract into the pyloric part of the stomach caused a flow of gastric juice, whereas if placed in the fundal part no such response was observed. Both of these observations suggest a specific endocrine secretagogue function on the part of certain areas in the gastric mucous membrane. A careful review of the literature will, however, show that this is by no means definitely established.

Let us examine the experimental evidence as to the specific formation or distribution of gastrin, the specificity of its physiological action and the specific chemical nature as far as it is known.

The Specific Formation or Distribution of Gastrin Activity.—As early as 1906 Popielski attacked the entire secretin theory, and since then has repeatedly contended that the experimental observations do not uphold the validity of such a theory. His work will be referred to again under the discussion on the intestine, but at this point it is desirable to call attention to his most sweeping and general conclusions. He considers a substance, "vasodilatin," not yet purified, to be very generally distributed in tissue extracts; and that this substance when injected causes any or all of the following physiological reactions—general excitability, convulsions, vomiting, defecation, urination, salivation, stimulation of gastric, pancreatic and intestinal secretions, an increased flow of bile, a fall in blood pressure and a decreased coagulability of the blood. It is clear that Popielski does not believe in any of the specific endocrine functions of the digestive glands, as they are usually considered at present, but rather that a certain physiologically active substance, "vasodilatin," is very

widely distributed and acts very generally. He has presented some physiological evidence to bear out this contention, but it is by no means convincing. Nevertheless, the other school has not been able to disprove his contention. Ehrmann (*b*) (1911-12) in part confirmed Edkins' views, in that he found extracts from all portions of the gastric mucous membrane to contain gastrin activity when assayed by injecting subcutaneously into Pawlow pouch dogs. He, however, also found duodenal mucous membrane to yield an active extract, but reported Witte's peptone, sodium nucleate, sarcosin, creatinin, alanin and glycocoll as inactive. Emsmann (1911-12) prepared extracts of tissues by taking one part tissue to two parts of N/10 hydrochloric acid and then after twenty-four hours heated to boiling, next diluted with water, neutralized with sodium hydrate, again acidified with acetic acid and then set aside under toluene until desired for use. Such extracts, when injected subcutaneously into Pawlow pouch dogs, reacted positively when prepared from mucous membrane taken from the pylorus, duodenum, jejunum, or ileum, and also from liver and pancreas tissue. Extracts from colon mucosa, spleen and submaxillary glands were inactive. He found none of these active when given by mouth. Z. Tomaszewski (*a*) (1913) in his first paper reports the extracts from pyloric and fundic mucous membrane as active gastric secretagogues in both normal and vagotomized dogs. In his later work, he added duodenal mucosa, hog gastric muscle, pancreas and large intestines as yielding active extracts, and considers it likely that "all organic extracts possess the power." He could not detect any difference in degree of activity of the pyloric and fundal areas of the gastric mucous membrane. At times he found Witte's peptone, when injected intravenously, to cause a sudden expulsion of gastric juice, but not what he would call an actual secretion, such as one observes after a subcutaneous injection of gastrin solutions. He considers this peptone action, upon which Popielski has laid so much stress, as a true vasodilating action and the gastrin action as that of a true secretagogue. He further concludes from his studies and from those of Labasow and Popielski, that Liebig's meat extract contains three active substances: one which stimulates the stomach directly when taken by mouth, another which causes a fall in blood pressure when injected intravenously, and a third which acts as a gastric secretagogue when injected subcutaneously. He further concludes that none of the extracts studied by him when introduced directly into the intestines, cause a gastric secretion unless it is through psychic factors. Keeton, Luckhardt and Koch, as a result of a series of comparative studies, conclude that gastrin activity may be extracted from all portions of the gastric mucous membrane of the hog, that about the same degree of activity is found in duodenal mucosa and in thyroid tissue and variable amounts may be obtained from liver and pancreas tissue. The spleen, thymus, brain, muscle, gastric juice, salivary glands and a carefully prepared fibrin peptone-proteose preparation were

uniformly inactive. They further found that the gastrin activity in these various extracts is not increased by using a pepsin hyprochloric acid digestion instead of a simple 0.4 per cent hydrochloric acid extraction. At times they found liver tissue to yield a very much more active product than the gastric mucosa, and at other times the reverse was true. The gastric mucous membrane has been found quite uniformly active, but the pancreas and liver vary considerably. Rogers, Rahe, Fawcett and Hackett (1915-16) find the activity in the alcohol soluble portions obtained from the non-coagulable or extractive fractions from parathyroid, thyroid, spleen, liver, pineal body and pancreas. In muscle, Witte peptone, pituitary and suprarenal they did not find the activity. Several other studies should be cited here, although they do not bear directly on the endocrine function of the stomach. Eisenhardt, Bickel, Djenab and Uhlmann have independently reported finding a gastric secretagogue in spinach. This also is active mainly when injected subcutaneously and appears to have many properties in common with the substance found in gastric mucous membrane.

Specificity of Action.—The work of Edkins and Gross, and of others, suggests that the physiologically active substance in gastric mucosa not only is specifically distributed, but that it also acts specifically as a gastric secretagogue, just as Bayliss and Starling (*a*) (*b*) (*c*) claim secretin acts specifically as a pancreatic stimulant. Popielski, however, as stated above, does not consider either specificity to exist. Neither school has definitely proven its case. Thus Mironescu (1910), in his studies on intestinal secretion from a Thiry-Vella fistula, found that extracts from gastric mucosa, salivary glands, liver and duodenum, act as intestinal secretagogues. Brain, pancreas, heart muscle and peptone he found inactive. These results favor Popielski's view, although the secretion noted may not have been the direct result of the injected substance, but a secondary one following a primary gastric or pancreatic secretion. Tomaszewski (*b*) (1918) observed that the subcutaneous injection of his preparations caused mainly a gastric secretion in Pawlow pouch dogs, sometimes a slight increased flow of bile, but only a very slight, if any, increase in the flow of saliva and no change in pancreatic secretion. He could, however, cause the pancreas to secrete more rapidly by introducing the extract intravenously; when thus administered he observed no effect on gastric secretion. The latter has been practically confirmed in the earlier work by Keeton and Koch (1915). In the earlier, as well as in their later work, Keeton, Luckhardt and Koch repeatedly found that the intramuscular injection of the gastrin product from gastric mucosa never caused salivation and, in a few crucial experiments, they were unable to stimulate the pancreas to secretion by the same mode of administration. In case one were to note a stimulation of pancreatic secretion, it might be due to the same secretagogue acting on both mechanisms, to a general vasodilator

action or, unless the proper precautions have been taken, it might be a secondary effect as a result of a primary gastric stimulation.

Specific Chemical Nature of Gastrin.—In view of various reports as to the physiological action and distribution of gastrin, as discussed above, the questions which may be asked as to chemical character of gastrin are: first, are gastrin and secretin the same; second, is there one and the same substance, vasodilatin, in all these extracts and is it the substance the physiological effects of which we are observing; third, is the active substance cholin or histamin?

If gastrin and secretin are the same they may possibly be protein hydrolytic products which might be Popielski's vasodilatin. According to the observations of Chizin (1914), purified peptone and proteose fractions do not possess the secretagogue action, and Keeton, Luckhardt and Koch (1920) found a carefully prepared pepsin digest of fibrin inactive, although it must have contained all stages of hydrolysis from proteose to amino-acids. Gastrin certainly is very much more stable than secretin. Secretin is very readily destroyed by dilute acids, alkalies and oxygen, but gastrin containing material can be boiled for hours in 20 per cent hydrochloric acid without any loss of activity and is extremely resistant in every way. It appears to be a basic substance, in that it can be extracted from alkaline aqueous solutions by amyl alcohol, and can then be recovered from the latter by dilute acid solutions. Like histamin and probably like secretin, it appears to contain the imidazol ring, it is precipitable by mercuric chlorid, alkaline silver solutions and by phosphotungstic acid. It differs from histamin, in that it is not precipitated by picric and picrolonic acids. It is not identical with cholin as its chemical properties show, and also, in that cholin has only a very slight secretagogue action. If it is not the same as vasodilatin, can it be separated therefrom? Maydell claims that by means of alcohol and ether precipitation, one can obtain a gastric secretin or gastrin free from the vasodilating ingredient. Tomaszewski considers the active substance to differ from the vasodilatin in Witte peptone, because he found, contrary to Popielski's claims, that 20 c.c. of a 5 per cent solution of the peptone when injected subcutaneously caused no gastric secretion, but that when the same dose is injected after adding thereto an active gastrin preparation a good physiological response follows. Nevertheless, as stated previously, Tomaszewski appears to believe that the active substance is very widely distributed. It is interesting to note that Eisenhardt (1910) finds the spinach secretin to behave chemically in many respects the same as the gastric stimulatory substance, that is, he finds it dialyzable, precipitated by phosphotungstic acid and by silver in the arginin-histidin fraction.

Mode of Action.—Although not yet obtained in pure form, still we have some light on this phase of the work. In the first place, the best response follows an intramuscular or subcutaneous injection, only a slight

one follows the intravenous injection and none the oral administration. The negative result, after the oral administration, cannot be due to destruction by pepsin in the stomach, as is evident from the studies by Luckhardt, Keeton, LaMer and Koch (1920). It may be destroyed in the intestines, however. Apparently the substance reaches the gastric cells humorally, if it really is a physiological process. When introduced through the femoral vein it causes a sudden expulsion of juice which is small in amount. This suggests that the substance is destroyed rather rapidly and probably in the venous system, or between the veins and arteries. Bickel (1917) reports that when he injected the spinach secretin by the femoral vein, both a secretion and a fall in blood pressure followed, but that when introduced directly into the mesenteric vein only the fall in blood pressure is observed. Djenab (1917) reports similar results with both spinach and duodenal secretin solutions, and he suggests that the liver neutralizes or destroys the active substance. It is barely possible that these observations explain in part how it is that the liver tissue varies so from time to time in gastrin content. Complete vagotomy, although it diminishes the secretion, does not prevent it. In Pawlow pouch dogs, the stimulating action of gastrin may be arrested by a definite dose of atropin, but it requires a greater dose to prevent secretion after gastrin than after or with a meal. All of these results suggest that the substance acts directly upon the cells and not on the nerve endings only.

General Conclusions and Clinical Application.—It is obvious that unless we obtain these substances in pure form we cannot hope to make an accurate, pharmacological and therapeutic analysis thereof. The purest extracts thus far prepared undoubtedly still contain considerable impurities, some of which may be responsible for certain general physiological reactions. The experimental studies by no means prove the endocrine function of the gastric glands, and there is no physiological evidence, at present, that a substance, gastrin, is normally elaborated in the usual physiological processes in the stomach mucous membrane. That being the case, there is no real organotherapeutic basis for the use of gastrin preparations in gastric disturbances. The author does not know of any clinical use of gastrin extracts, but, if it is to be employed at all, it should be injected intramuscularly or subcutaneously; by mouth it is worthless, and intravenously it is very dangerous, due to the marked depressor action.

Intestinal Endocrine Function

In 1896 Popielski first showed that the introduction of 0.4 to 0.5 per cent hydrochloric acid into the duodenum causes a flow of pancreatic juice. This was interpreted by him to be due to a stimulation of nerve endings in the duodenum and thus the secondary stimulation of the pancreas.

This view was soon considered incorrect, first, because of similar results with all nerve connections supposedly cut, and, second, in view of the secretory effect of intravenously introduced acid extracts of the duodenum, as first shown in 1902 by Bayliss and Starling (*a*). Popielski, however, called attention to the general distribution of this activity when acid extracts of tissues are made; and claimed that we are not here dealing with the action of a true specific secretagogue, but with a general vasodilator phenomenon due to a substance he called "vasodilatin." Many of the earlier workers were inclined to consider cholin as the truly active constituent, but in recent years the evidence appears to be distinctly against that view, and tending to acceptance of the view that the active substance may be betaimidazolethylamin or histamin. We can summarize the studies on this subject most satisfactorily under the following headings: (a) specificity of distribution of secretin activity; (b) specificity as to site of action; (c) specific chemical character of secretin; (d) physiological evidence as to the presence of secretin in the blood and as to its mode of action; (e) relation of secretin to the internal secretion of the pancreas; (f) other supposed physiological actions; (g) clinical applications.

Specificity of Distribution of Secretin.—Bayliss and Starling (1902) found the secretagogue activity in preparations of the duodenum, somewhat in the jejunum, almost absent in the ileum and entirely absent in the salivary glands, liver, spleen, pancreas, kidney and tongue; but one must bear in mind that all of their studies were conducted on anesthetized animals. Furthermore, in an attempt to meet Popielski's criticism, the authors tried to remove vasodilatin by absolute alcohol extraction and then used the alcohol insoluble residue as a purer form of secretin. In this process they neither removed the vasodilatin or depressor action completely, nor are they certain that they did not also remove some of the true secretin in the alcohol extraction process. In fact, the purer secretin solution not only showed a less marked depressor action, but also a distinctly lowered secretagogue activity. Camus (1902) reported that large doses of an acid maceration of mesenteric ganglia from the rat stimulated the pancreas to secretion. Popielski claims that all blood pressure lowering extracts, if they cause a vasodilatation together with decreased coagulability of the blood, bring about the same secretion. It is, of course, well known that most of the tissues when extracted with dilute acids or water yield a blood pressure lowering solution, nevertheless Popielski has by no means satisfactorily confirmed his claims by experimental observations. Matsuo reports results similar to those of Bayliss and Starling and adds that Witte's peptone, heart muscle, kidney and lung extracts are inactive. F. Sodre and G. Stodel find the absolute alcohol extracts of Witte's peptone in doses of 0.02 gram per kilo bodyweight to cause no appreciable secretion as compared with duodenal secretin solutions. They also found commercial silk and egg peptones equally inactive. Rogers, Rahe, Fawcett

and Hackett (*a*) (*b*) (1916) reported that the aqueous extracts prepared from liver, when injected subcutaneously, cause a very vigorous pancreatic secretion. It is, however, not certain whether this secretion is a direct effect, or secondary one due to a primary gastric stimulation. They found thyroid and thymus to yield less active extracts and pituitary and parathyroid were inactive. These authors used dogs with permanent pancreatic fistula for their physiological tests. Uhlmann (1918), as a result of a series of studies on the physiological effect of "orypan," a commercial vitamin preparation prepared from rice polishings, arrives at very sweeping conclusions as to the pharmacological action of the antineuritic vitamin. He finds that this extract, when injected intravenously in the rabbit, causes salivation, and that the subcutaneous, intravenous or oral administration stimulates the gastric and pancreatic secretions. He concludes that it acts mainly on the parasympathetic nervous system, secondary on the digestive glands, and lastly that it causes an increased tone of the musculature of the entire body. He finds this activity distributed in rice polishings, spinach, nettles, meat, oats, yeast, clover and cabbage. He further found atropin to inhibit all of these physiological responses. These studies, together with those already cited under gastrin, do not by any means clearly prove either side of the controversy between Bayliss and Starling on the one hand and Popielski on the other. It is evident that the isolation of the pure substance, together with careful quantitative physiological studies on unanesthetized animals, are the only means of definitely deciding this important question.

Specificity of Action.—Here the evidence is on the whole by no means clearly in favor of the Bayliss and Starling school. Favoring their view, we have many negative reports on pancreatic secretion with gastrin preparations, as already discussed above; also some negative results as to gastric and salivary secretion following the injection of secretin, as shown by Bayliss and Starling and Dale and Laidlaw and, lastly, the *in vitro* studies suggesting a specific action of pancreas tissue on secretin.

Under the discussion of the specific distribution of gastrin activity, it was shown that acid extracts of the duodenal mucous membrane had been found, by various observers, to cause gastric as well as pancreatic secretion. It is, of course, possible, but not very probable, that the positive results as to gastric secretion may have been the secondary result of a primary pancreatic secretion. Still other secretions have been found to be stimulated by extracts thus prepared from duodenal mucous membrane. Thus Alessandro (1912) finds such an extract to stimulate the flow of lachrymal fluid. Frouin finds it to cause a sudden and marked secretion of intestinal juice. Botazzi and Gabrieli (1905) find this stimulating effect also, but that it continues over a longer time period. Downs and Eddy (1919) found that the intravenous injection of a secretin solution stimulates the flow of bile very decidedly, and they also noted a marked

increase in the number of white and red corpuscles in the blood in rabbits. Thus, 0.01 gram of a dried acid extract per kilo bodyweight after fifty minutes caused an increase of 44.2 per cent in the white corpuscles and 17.07 per cent in the erythrocytes, and this persisted for an hour or more. They also noted that rabbits, previously starved for forty-eight hours and then fed cabbage water and oats, showed an average increase of 76.7 per cent in the white corpuscles and 18.65 per cent in the erythrocytes with the maximum effect 3.2 and 1.9 hours after the meal. Lambert and Meyer (1902) find secretin to act almost equally well on salivary and pancreatic secretions. Piticariu reports the increased flow of urine as a result of duodenal secretin preparations. It is, of course, possible that some of these other physiological effects may be due to impurities in the secretin solutions, but until this is proven to be the case these facts should be borne in mind. In the discussion under peristaltic hormone, it will be seen that possibly one and the same substance may be causing both secretion and peristalsis.

A few *in vitro* studies suggest a specific affinity on the part of the pancreas tissue for secretin. Thus, Hamill and Dixon (1908-9) find that the secretin activity can be destroyed by incubating solutions thereof with various tissues, but that in this respect the pancreas is so very much more active than other tissues that it can almost be considered a specific action. They found that a definite amount of pancreas tissue is capable of destroying only a definite amount of secretin. Liver tissue also appeared to have a specific affinity for the secretin, but in this case the secretin activity could be recovered by extraction of the mixture; in other words, the secretin did not appear to be destroyed in this case. Hamill and Dixon considered that the secretin converts a prozymogen form of the enzymes into a zymogen form, and that it is destroyed in this process just as epinephrin is destroyed when it acts physiologically. The authors also observed that the flow of pancreatic juice, brought about by the intravenous administration of secretin, could be arrested by an injection of pancreatic emulsion, especially if the latter was injected before the injection of the secretin. Lalou (1912) in part confirmed these observations. Delezenne and Pozerski (1904-1912) report that a 0.9 per cent sodium chlorid solution is very efficient in extracting secretin from duodenal mucous membrane, providing it is boiled immediately after the extraction. They conclude from their studies that if such extracts are not heated the secretin is rapidly destroyed by the proteolytic enzymes present in such an extract; and that the reason a 0.4 per cent hydrochloric acid solution is a good extraction medium is because it inhibits the action of these proteolytic enzymes. It is barely possible that the supposed destructive action observed by others in pancreatic tissue may be due to the same factor. Hamill and Dixon observed that boiled pancreas extracts do not possess the destructive action and that secretin aids the entero-

kinase in activating trypsinogen. This observation suggests a ferment action but, on the other hand, they observed the relation between secretin and pancreas to be a quantitative one and not a catalytic one.

Specific Chemical Character of Secretin.—Is duodenal secretin the same as or different from gastrin, histamin or vasodilatin in chemical characteristics? The chemical properties of gastrin have already been discussed and the studies thereon suggest that it is not identical with duodenal secretin. The most specific studies on duodenal secretin show that it is very easily oxidized, easily destroyed by bacteria, acids, bases, and by proteolytic enzymes. Certainly, no such labile character can be ascribed to gastrin.

Is secretin identical with histamin? The fact that fair evidence has been obtained, indicating the presence of histamin in duodenal mucous membrane, has led some to conclude that histamin is identical with secretin and that it is the vasodilatin of Popielski. Thus Barger and Dale (1911) separated from duodenal mucosa a picrat "quite similar to histamin picrat," with a melting point of 232° C. The product gave all the physiological reactions of histamin and the authors suggest that it probably is a constituent of Popielski's vasodilatin, but that it is not necessarily identical with duodenal secretin. Mellanby and Twort (1912) found organisms which form histamin from histidin in the intestinal contents from the duodenum downward in the guinea pig, and consider the origin of histamin in the intestinal wall, as due to the action of these organisms. Berthelot and Bertrand (1912) also isolated an organism from the human intestine which produces histamin from histidin. Recently Abel and Kubota (1919) from their studies conclude that histamin may be obtained from many tissues and, in fact, consider it to be one of the building stones in proteins because they obtained evidence of its formation in the acid hydrolysis of casein and edestin. Their evidence is in part chemical and in part biological, and they conclude that the motilines, vasodilatin and "histamin-like" substances in tissues are all one and the same substance—histamin. Their work has not been confirmed thus far. Even if histamin is obtained by extracting the tissue in question, and even though histamin does possess the secretagogue and other physiological properties attributed to gastrin and secretin, the all important fact remains that the secretin activity from duodenal mucous membrane, although it appears to give many of the color and precipitation reactions of histamin, still appears to be very much less stable.

Are secretin and vasodilatin identical chemically? It will be remembered that Bayliss and Starling tried to prepare their secretin free from depressor action. The general impression seems to be that they succeeded, but a careful examination of their tracings showing the blood pressure and secretory effects reveals that with lowering of the depressor action in their extracts they also lowered the secretagogue activity very

distinctly and furthermore that they never obtained an active secretagogue free from depressor action. Many have assumed that the absolute alcohol extraction, as applied by Bayliss and Starling, is efficient in removing the vasodilatin action without actually proving it to themselves. Certainly absolute alcohol extraction is not efficient in making a clear cut separation of gastrin from vasodilatin activity, and probably the same is true for secretin and vasodilatin. Hamill and Dixon laid considerable stress on preparing their extract free from vasodilatin, but they do not publish data showing the extent to which this was done. Dale and Laidlaw (1912) employed an entirely different method by means of which they claim to have obtained a product which "has a powerful secretin action and is relatively free from depressor substance." They could precipitate their substance by picric acid. Their work was reported in a very brief article, and no further confirmatory evidence from them has come to the notice of the writer. Launoy and Oechslin (1913) report that by repeated reprecipitation with absolute alcohol they obtained a very active preparation, and a blood pressure tracing taken therewith shows it to be free from depressor action, but with good secretagogue action as a result of the same dose. They apparently obtained a vasodilatin free secretin preparation. Their description of the method employed is, however, so brief that it will be very difficult to confirm their findings. A further study by them led them to the conclusion that a difficultly soluble picrolonat mixture may be obtained. From this mixture they obtained three fractions, one consisting of red octahedral crystals melting at 262° C., another consisting of needles "similar to histamin picrolonate melting above 300° C.," and a third fraction, very active as a depressor substance and possessing some secretagogue activity, but not as active as "other extracts or depressants." As stated before, some of the older observers considered it probable that secretin is nothing other than cholin and that cholin is Popielski's vasodilatin. Von Fürth and Schwarz (1908) concluded that cholin is present in the Bayliss and Starling secretin preparation, but that only a part of the secretagogue action therein is due to cholin. Le Heux (1918), on the other hand, finds that extracts from the intestinal mucosa contain sufficient cholin to account, in a measure, for the peristalsis stimulating power upon the intestinal musculature. As previously stated, under the discussion of the specific distribution of secretin, Uhlmann (1918) takes practically the same view as Popielski as to the general action of secretin, only he takes a still broader view as to the site of action and distribution. He considers the antineuritic vitamin to be such a substance. Jansen, however, claims to have shown that this vitamin and secretin are not identical.

The preponderance of evidence certainly is in favor of the view that secretin is not the same as gastrin, histamin or cholin, but we are by no means certain that it is not a depressor or vasodilatin.

Physiological Evidence as to the Presence of Secretin in the Blood and as to the Mode of Action of Secretin.—In 1902 Wertheimer (*a*) (*b*) first showed on the dog that when dilute hydrochloric acid is placed in the duodenum and blood is then taken from the mesenteric vein and injected into another dog the latter is stimulated to secrete pancreatic juice. Wertheimer and Lepage (1902) found that ligation of the thoracic duct did not prevent pancreatic secretion in a dog when dilute hydrochloric acid is placed in the duodenum. Popielski considers this to favor the view that the stimulation of the pancreas is not humoral, but rather a reflex nervous one. Fleig confirmed these findings, but did not consider them to disprove the humoral theory. Enriquez and Hallion (*a*) (*b*) (1903) also showed that the injection of carotid blood from a dog stimulated to pancreatic secretion by placing dilute hydrochloric acid in the duodenum causes a flow of pancreatic juice in the recipient. Popielski (1907) confirmed the findings of Enriquez and Hallion, but considered the effect upon pancreatic secretion too slight, and that the partial asphyxia brought about by the anesthetic may cause the same effect. His experimental evidence is by no means convincing. Hustin (1913) showed that electrical stimulation of the duodenum or of the pancreas does not cause pancreatic secretion, but that perfusion of the isolated pancreas with blood when acid is in the duodenum does cause a secretion. Like Hamill and Dixon, he considers the pancreas to remove the secretin from the blood. Matsuo (1913) reports fairly satisfactory results in four out of eight experiments by the transfusion of blood from one dog to another having dilute hydrochloric acid in the duodenum of the donor. The failures he considered as due in part to cases in which the blood pressures were not the same in the two dogs and, in part, to the prevention of transfusion due to coagulation of the blood. He also confirmed Wertheimer's experiments referred to above. On the whole, the evidence here is distinctly in favor of the humoral theory of pancreatic stimulation. However, how is secretin formed? Is it formed in the intestinal contents by the acid chyle and then absorbed, or is it formed in the duodenal wall? The observations made in attempting to answer these questions are very interesting. Direct introduction of neutral secretin solutions into the duodenum does not cause secretion. This has been shown by Bayliss and Starling (*a*) (1902), Wertheimer and Dewillier (1910), Matsuo (1913), and others. Very likely these negative results are due to the destructive action of proteolytic enzymes on secretin. It is well known that both pepsin and trypsin destroy it. Carlson, Lebensohn and Pearlman (1916) demonstrated this for gastric juice, and others, as described previously, have demonstrated its destruction by proteolytic enzymes in alkaline or neutral solutions. Popielski (1907) showed that if dilute hydrochloric acid be left in the duodenum for some time and this then removed and injected into another animal, no stimulation is observed. He claims, however, that pancreatic

juice, when similarly injected, does cause a secretion, whereas if introduced into the intestines it requires the addition of an acid in order to act as stimulant to pancreatic secretion. Aqueous extracts of duodenal mucous membrane, when injected intravenously, were found very efficient by Popielski, whereas the simple introduction of water into the intestine did not cause a pancreatic secretion. He also found ordinary fats containing small amounts of free fatty acids to stimulate when placed in the duodenum. He interprets his findings as proof of a stimulation of nerve endings in the duodenum, and thus reflexly a stimulation of the pancreas. The evidence on the whole is, however, favorable to the humoral path of stimulation. But there is no evidence proving the actual formation of secretin in the duodenal contents. If it is formed it is due to acid acting on the mucous membrane of the duodenum and causing the formation of secretin in the intestinal wall.

Many of the earlier observers reported that atropin does not inhibit pancreatic secretion when it is brought about by secretin or by dilute acid acting in the duodenum, whereas the secretion brought about by cholin can easily be inhibited by atropin. Popielski (1907) and Uhlmann (1918) have, however, shown that when the doses are properly adjusted one can inhibit the secretion in either case. This is very likely correct, in view of similar observations by Luckhardt, Keeton and Koch (1920) on the effect of atropin on gastric secretion as brought about by a meal, by gastrin, or by histamin. It is very likely entirely a question of the relative doses of secretin and atropin employed. Such is at least the case as to gastric secretion. The fact that atropin may inhibit the action of secretin does not necessarily invalidate the humoral theory, for atropin acts on cells directly as well as on the nervous system.

Relation of Secretin to the Internal Secretion of the Pancreas.—Very soon after the discovery of secretin action many attempts were made to establish a relationship between the duodenum and the internal secretion of the pancreas. A number of studies were conducted in which it was attempted to show a decreased prosecretin content in duodenal mucous membrane in cases of diabetes mellitus and in depancreatized dogs. It is obvious that the two conditions are by no means identical. Bainbridge and Beddard (1906) found very little or no prosecretin in five out of six cases of diabetes mellitus. Later, however, Bainbridge (1908) found prosecretin present without doubt in eight out of nine cases of human diabetics; only one case of diabetic coma, a seventeen-year-old boy, yielded an extremely weak secretin solution. The authors also were not able to influence the prosecretin content of the duodenum in dogs by acid poisoning, nor by extirpation of the pancreas. Evans (1913) found a loss of 33 to 95 per cent in the secretin concentration obtained from the duodenal mucous membrane after removal of the pancreas. The higher loss occurred six days after the operation. In one dog 1/6 of the pancreas

was left intact, but no pancreatic juice was permitted to enter the duodenum. In this case glycosuria did not develop although the animal became emaciated and his duodenum still contained the normal amount of prosecretin. Evans concludes that the loss of the pancreatic juice is not responsible for the loss of prosecretin, but that it is due to the loss of the internal secretion. Hedon and Lisbonne (1913) report that removal of the pancreas does not affect the prosecretin content of the duodenum in three to twenty-five days after the operation. Pemberton and Sweet (1901) arrive at similar conclusions. It is very doubtful indeed whether the extraction method for secretin is to a sufficient extent quantitatively developed to be of use in determining slight changes in prosecretin content; and the physiological assay of such extracts is also very likely to lead to erroneous results, especially if carried out on anesthetized animals.

A number of very indefinite conclusions have been reached following the removal of the duodenum. Thus Pflüger (1907) found complete removal of the duodenum in frogs to cause a more severe glycosuria than complete removal of the pancreas. He also reports that destruction of the nervous connections between the duodenum and pancreas causes a glycosuria. Rosenberg (1908) reports that similar operative procedure in dogs does not always cause glycosuria. Zack (1908) reports that in two cases of suicide in which the duodenum had been injured by corrosive poisoning, glycosuria was observed. A similar corrosion of the esophagus and stomach led to no glycosuria, but an experimental corrosion of the duodenum caused glycosuria. Gaultier (1908) destroyed the duodenal mucosa by incision and by cauterizing with silver nitrate in two dogs, and observed glycosuria in both cases. Minkowski (1908), however, reports temporary glycosuria following complete removal of the duodenum and partial pancreatectomy. Four weeks later the remainder of the pancreas was removed and the usual severe glycosuria set in at once.

Finally, we have the attempts to use secretin solutions as a therapeutic measure in diabetes mellitus. Thus Bainbridge and Beddard (1906) gave 90 c.c. of secretin solution daily by mouth in each of three mild cases, and observed no beneficial effects. Moore, Edie and Abram (1906), in the first studies, obtained fair results in three out of a total of five cases, but in a more extensive series later most of the results were negative. Nellis B. Foster (1907), with nine cases, and Charles (1906), with three, reported entirely negative results. Croftan (1909) obtained favorable results in one case and Dakin and Ransom (1907) report a temporary beneficial effect in one case, but even after twelve weeks' treatment, the glycosuria was as severe as before. In view of the destruction of secretin by gastric and pancreatic juices it certainly is not justifiable to give secretin by mouth. The results obtained clinically fail also to warrant the further use of secretin in the treatment of diabetes mellitus.

Clinical Application of Secretin.—The clinical use of secretin preparations has been recommended by various physicians and manufacturers, but never on a good scientific basis, nor on experimental observations. In the first place, the products on the market do not appear to be physiologically tested, let alone standardized, and in the second place, practically all of the products are recommended to be given by mouth. As already stated, this mode of administration is not physiologically sound. The only efficient method of experimentally demonstrating secretin activity is to employ the intravenous injection. This, however, is hazardous clinically with an impure, unstandardized extract as we have to deal with in the case of secretin. Simon (1907) made a careful study of the effect of the repeated injection of a secretin solution prepared according to Bayliss and Starling. In one dog he observed a violent reaction resulting in a bloody diarrhea almost immediately after the injection. At autopsy the intestines showed a general bloody appearance and the capillaries were considerably dilated. In two other dogs repeated injections over a period of ten days and four months respectively, usually were followed by an intermittent myxorrhea and later by a chronic form thereof. Histological examination showed that one injection brings about a gathering of eosinophiles to the surface of the intestines and almost a complete depletion thereof in the bone marrow and spleen.

In spite of the contra-indications as to the oral administration of secretin, a number of clinicians report favorable results therewith in pyloric stenosis, pancreatic insufficiency, as a hepatic stimulant, and as a stimulant to peristalsis in colonic stasis. Beveridge claims to have obtained good results in more than a hundred cases. Ewald obtained a favorable result in one out of thirteen cases, and Harrower (*a*) (*b*) recommends its use in many digestive disorders. Carlson, Lebensohn and Pearlmann (1916) give a very good summary in their paper on the therapeutic value of secretin, and they show very clearly that the commercial secretin preparations "secretogen" and "duodenin" are free from both secretin and prosecretin.

Motilin or Peristaltic Hormone.—A frequent response following the injection of either gastrin or secretin preparations is increased gastric and intestinal motility. Weiland (1912) observed that the immersion of rabbits' intestines in Tyrode's solution at 38° C. yields an extract which, by direct contact with another intestine, causes a contraction. He found this activity in the stomach and small and large intestines. Spleen, muscle, heart, liver, brain and kidney extracts acted inconsistently or negatively. The active substance appears to be very similar in chemical properties to gastrin, histamin and secretin. The most purified product, as used intravenously on the rabbit by Weiland (1912), caused no salivation, no fever, and no flow of tears, but diarrhea, segmentation and peristalsis. In the dog, a fall in blood pressure was noted together with

marked defecation, but otherwise none of the "other effects of vasodilatin." Weiland considers the substance to be of physiological importance in the automatic movements of the intestines, through stimulation of Auerbach's plexus. As previously stated, Le Heux considers the cholin content of intestinal extract to be sufficiently high to account to a great degree for the action of such extracts on the intestinal musculature. Zuelzer (*a*) (*b*), Marxer and Dohrn (1908) first prepared a peristaltic stimulant from the stomach mucosa, but later used spleen instead. This spleen preparation has been placed on the market as "hormonal" and has been used clinically to some extent. Weiland considers the active ingredient in "hormonal" to be identical with the substance he detected in intestinal extracts. Berlin (1908) also studied spleen extract prepared by himself and concluded that the active ingredient is neither cholin nor histamin, but a third new substance. This substance may or may not be identical with gastrin or secretin. At present we can safely say that it is very similar chemically to histamin, gastrin and secretin, and physiologically there appears to be some relation also. Zuelzer (1910) has introduced this extract into therapy in the treatment of obstipation. Several have reported favorably thereon, while others consider it worthless and even dangerous, in that its intravenous use has caused death in several cases. Forkel, Kretzchmann (1912) and Zuelzer (1910) report favorably as to its clinical use. Sabatowski (1912) considers it worthless. Uhlmann (1918) and Popielski (1912) consider the peristaltic response to be simply one of the many due to one and the same substance. This substance appears to be the antineuritic vitamin according to Uhlmann, and vasodilatin according to Popielski.

SECTION XIII

Disorders of Metabolism and Internal Secretions in Relation to the Eye . . . . . *Percy Fridenberg*

Introduction—Ophthalmology and Endocrinology—Sex and Heredity—Phylogenesis of Ophthalmo-Endocrine System—Ophthalmic Neuro-Endocrinology—Ophthalmo-Biology—Cataract—Corneal Changes in Senility—Ocular Pigment—Ocular Physiology—Winking and Tear Secretion—Intra-ocular Tension in Relation to Nutrition and Secretion—Ocular Morphology—The Thyroid Eye—The Pituitary Eye—Ocular Vagotonia—Cycloplegics in Eye-Strain—Ocular Sympathetico-tonia—Ocular Symptoms in Exophthalmic Goitre—Hormone Deficiencies and Ocular Affections—Ocular Affections of Pituitary Origin—Ocular Disturbances in Hypophyseal Disease—Hereditary Optic Nerve Atrophy—Vascular Disturbances—Uveitis—Skin Affections of the Eye—Phlyctenular Keratitis and Conjunctivitis—Lymphatic States—Vitamines and the Visual Organ—Endocrine Therapy in Ophthalmology—Ophthalmic Pharmacodynamics—Endocrine Therapy—Seasonal Incidence.

Disorders of Metabolism and Internal Secretions in Relation to the Eye

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NEW YORK

Introduction

Endocrinology is of basic and wide significance for all vital reactions. The processes of heredity, including sex, the rhythm and periodicity of growth and maturity as well as of senescence, are largely controlled by the hormones, although the mechanism and the details of that control are as yet not fully understood. An application of this science to clinical ophthalmology may follow either of two paths. We may compile and codify the data of ocular disease, morphology, and immunity, and note the reciprocal relations with admittedly endocrin states or disturbances. Or, we may attempt to trace back to comparatively uncomplicated biochemical reactions both the ophthalmological observations and those concerning the glands of internal secretion. This would appear to be the more scientific method of attack at least in any preliminary study hoping, as does this one, rather to map out a field for further investigation than to offer detailed and definite conclusions and suggestion for therapy and diagnosis. Endocrinology influences heredity, morphology, metabolism, immunity, development, function and nutrition, and its application to any special field of medicine must logically relate and refer to one or more of those categories.

Knowledge of the basic facts of endocrinology has given an entirely new significance to the terms constitutional treatment and systemic disease. We think of it less in terms of complement fixation, mixed treatment, plasmodial parasitism, the salicylates, than as dominant dyscrinism adrenal, thyroid, pituitary or combined, with a final clinical picture, as far as symptoms go, of vagotonia expressed in spasmophiliac reactions, or in sympatheticotonia. These can be modified not only by drugs and diet, but by vitamins and hormones, alimentary and emotional regimen, and exercise. This science shows us, further, that all telluric influences,

climate, heat and cold, inheritance, race geographic conditions, seasons and sunshine, mothers' milk and materies morbi, act largely, in the last analysis, through a previously unrecognized link in the chain of cause and effect, the glands of internal secretion.

Ophthalmology and Endocrinology

A priori one might expect endocrin implications in ophthalmology from two standpoints. If the glands of internal secretion have a proven influence on structure, development, physiology, immunity, emotion type, and temperament, surely there must be some indications, normal or morbid in an organ which is so peculiarly suited to clinical observation and to the study from day to day of symptoms, disease processes, and reactions to drugs and treatment, and one which indicates in so many ways its interrelations with systemic conditions and disturbances. Endocrinology suggests ophthalmic applications.

The eye presents such significant and characteristic peculiarities and individualities depending on race, age, sex, life epoch, skull and orbit form, emotion, neurovascular fluctuations, that ophthalmology suggests endocrin influences.

Of all organs of special sense the eye shows most strikingly a connection with the endocrin system and dependence on the double system of vegetative control of vagus and sympathetic. This is shown in details of structure and biomorphology, function in health and disease, and perhaps most dramatically and pregnantly in its response to organotherapy or in the striking reactions to alkaloids and drugs which in addition to their local action referable to either of the dominant branches of the vegetative nervous system have a definite selective action on one or the other gland of internal secretion. In this sense the organ of taste, like that of smell, is of relatively negligible significance, residing as they do in an almost structureless area which is merely a specialized mucous membrane which has hardly the structure or the other criteria (developmental, neurological, metabolic) of an independent organ. The sense of hearing, too, is akin to the eye in its phylogeny as a mechanism mediating the perception of distant objects which may let loose neuromuscular reactions in the organism. The ear, however, as far as it has hitherto been made the subject of histological and clinical study appears to lack altogether those typical reactions of sympathetic irritation which make of the eye an organ *sui generis* for the expression of the emotions as it is primarily the medium by which those emotions are aroused and, perhaps, harmlessly discharged or canalized by an action which suggests the safety valve in effect if not in detail. In this last connection the reaction of the pupil to sensory and psychical stimuli is significant, as is

that of the secretion of tears under sympathetic irritation, and possibly, although to a much lesser degree, the unconscious and reflex opening and closing of the lid-fissure which is but one form of the wink.

Many of the most suggestive and at the same time the most definite data in endocrinology have been gained in the biological laboratory, in morphologic experiments on lower animals, and in exact and detailed studies of nutrition, basal metabolism, and growth. This is significant both for the essential correctness, validity and fundamental nature of the principle and for the wide field of its application in bio-physiology. On the other hand this very fact indicates that much further study in a different field is required before all the observations can be applied to man and the clinic, to the patient in the bed, and that we have not as yet a complete and ready-made formula of endocrin therapy, or, in fact, of completely detailed and thorough endocrin diagnosis.

Normal development has little or nothing to do with functional activity or with trophic nerve influence (Uhlenhuth). Nutrition, depending on circulation and on the oxygenation, calcium and magnesium content, and tonicity of the nutritive media, is the main factor.

Biologic studies and clinical observations show a dependence of ocular development on nutritional states which can be modified by diet, vitamins, and endocrin extracts. Striking in the extreme case of the laboratory experiment, these conditions must be mirrored, less typically and extremely, perhaps, in the endocrin variations within the limits of every day life. Stockard has shown that merely altering the degree of oxidation of the embryonic organism leads to marked developmental defects and to the production of monsters controllable in detail of their variation from normal.

Acidity and alkalinity, basic biologic conditions, are important in eye development, and it is at least probable that these states are connected with dominance of one or the other endocrin gland or at least indicative of a final dominance of one or the other of the two antagonistic systems of vegetative nerve control, the vagus and the sympathetic.

Race and Heredity.—The color of the iris is a distinctive feature and there is a typical eye for each race. (Nordic, Hebraic, Negroid, Mongolian, Amerind).

The brown iris is a dominant Mendelian characteristic, suggesting that dominant features, such as black hair and eyes, cataract, squint, supernumerary digits, are vagotonic or chromatrotrope.

Skull-form, dolicho-brachy-cephalic is a criterion of race. Its influence on the size and shape of the orbit, hypsi-conchae, chamai-conchae, (Stilling) and the production of long or myopic and short or, hyperopic, eyes is associated with the development of the pituitary and the spatial relations to the region of the sella. Morphologic peculiarities, develop-

mental aberrations, possibly inherited neuroses, may be secre-togenic. This might throw light on "maternal impressions."

Internal secretions of the five important endocrin glands, pituitary, suprarenals, gonadal, pineal, and thyroid, control racial characteristics of the great divisions of man, Caucasian, Negro, Mongol, Amerind (?).

Inheritance as a morphological process met with certain serious objections based entirely on quantitative considerations of size of ovum and spermatozoon. A secreto-genic and secreto- or glandulotropic influence would be more acceptable and in greater logical accord with topographic possibilities. Summation of endocrin sensitizing proteins again would account for inheritance of certain acquired characteristics, i. e., those which by their nature would affect the physiological, endocrin balance, while it would explain the failure to transmit purely mechanical alterations such as amputations either of extremities or of foreskins.

The same summation via consanguinity of parents would produce a bad inheritance, or what we might call an endocrin overdose, and thus account for many familial degenerative processes and developmental defects. The incidence of such ocular degenerations with a history of marked dietary or vitamine insufficiency during the pregnancy of the mother is at least significant.

The familial or what is analogous, racial element, is seen in glaucoma, in retinal, corneal, lenticular, and other degenerative states. Vitamin deficiency or hormone lack due to syphilis or tuberculosis destroys vision and pigment and gravely affects the endocrin glands which then show in the offspring a similar disturbance of nutrition.

Sex and Heredity.—Sex and other processes of heredity are endocrin reactions linked to the chromosomes (Goldschmidt). The fertilized egg protoplasma furnishes the chemical material for growth and differentiation, while the chromogen furnish determinants and factors for specific direction of processes which make offspring resemble their progenitors.

These factors are enzymes of specific characteristics in quality and quantity or concentration. The velocity of the enzymes, which is proportional to their concentration, stabilizes the rhythm of differentiation. The principal reaction thus accelerated by enzymes of heredity to a definite velocity is the formation of hormones directing growth, differentiation, periodic development, with an action similar to that of the glands of internal secretion.

Phylogenesis of Ophthalmo-Endocrine System

Endocrin control has developed biogenetically in response to repeated stimuli depending on sense impressions, largely visual, and auditory, producing characteristic activation patterns (Crile) in man and animals. The internal secretions called hormones precede all types of nervous sys-

tems in visceral control (Starling), while the central nervous system controls those organs which have been added more recently.

Of sense organs, the first was taste, then smell, then hearing. Sight, the most important sense, came rather late with development of higher cerebral faculties (Mayo). Even memory is largely visual in most persons. (Mayo).

The sympathetic nerve system is the more primitive, in connection with the endocrins, and there is autonomous action of non-striated muscle in gut, heart, uterus, possibly in the iris.

Ophthalmic Neuro-Endocrinology.—The eye is one of the most important, prolific, and basic sources of those activation patterns to which Crile attaches so much significance as the adequate stimuli for activation of the ductless glands and the production of the emotional secretions, adrenin and thyroxin.

The delicate reaction of the pupil to emotional and vascular states and to the action of alkaloids is hardly equalled by the heart, which it surpasses in its accessibility to observation and experiment.

The pupillomotor action of alkaloids is the touchstone of their physiological action, and at times of their chemical constitution.

Lid-closure (winking) and tear-secretion are largely purposive processes controlled by nervous influences. That means, now, vegetative states.

The double control of vagus and sympathetic is expressed exquisitely in the innervation of the iris, the sphincter relating to the former, the dilatator pupillae to the latter, system, in logical accord with the control of ring and longitudinal muscles in intestine, stomach and bladder, and, possibly cardiovascular apparatus.

This control extends, also, to prominence of the globe, comparative wideness of the lid-fissure, rate of winking and of tear secretion, and not improbably, to intra-ocular tension.

The importance of an endocrin organ is measured, in part, by the degree of its control by the sympathetic (Crile). From this point of view, the eye may well be considered an organ of internal secretion, having in mind the aqueous as a biological secretion which is notoriously subject to emotional variation, in addition to the manifest external secretion, the tears, and the marked dependence of the pupil on secretogenic states, and its interdependence with the heart action (Aschner reflex).

The pupillomotor alkaloids which ophthalmologists know as mydriatics and meiotics, are typically and characteristically marked by diametrically opposite action on the two vegetative systems.

The development of emotional predispositions takes place under the influence of activation patterns (Crile) arising from sensory impressions, largely visual, as purposive adaptations of the organism (fear, anger, love, etc.) in man and animals. Influence of nutrition and mode of life

on endocrin balance may well account for the disposition of the tiger, the ox, and the horse, and disposition here means that one tends to produce adrenalin, the other thyroxin.

Defensive states and defensive reactions are mediated by recognition of danger at a distance by the eye, and conversely, the eye is the index of the emotional state, fear, rage, or desire.

Habitual emotion means temperament and character, as habitual gesture becomes expression, and the glance or look is, finally, looks (cf. visage, vultus, gesicht, prosopon).

Ophthalmo-Biology.—*Ocular Malformations and Degenerative Processes.*—The normal incidence and rhythm of all biologic processes seems to depend largely on the inheritance and continued balanced action of hormones and of vitamine supply. A review of ocular malformations and degenerative processes cannot leave these factors out of consideration.

Such dramatic situations as those presented by myxedema, cretinism, and tetany, and the grave disturbances in organic functional processes caused by operative removal of ovary and testis, indicate sufficiently the importance of that balanced interrelation of the glands of internal secretion for which we may coin the word eucrinism.

So far but little attention has been paid to ophthalmic implications of these conditions, but data are at hand, mainly from animal experimentation which throw some light on certain well known and definite disturbances of ocular function, form, and nutrition, and show a fruitful field for further study.

Most of the transmitted defects of the eye follow Mendelian rules and, with the exception of those which are sex-linked, would appear to be dominant characteristics.

The eye and its appendages would appear to be unusually subject to developmental defects and congenital disease. This attribute has been explained by the great diversity of histological elements concerned in the structure of its numerous tissues, a diversity which may in part account for the fact that the rudimentary deposit (anlage) of the eye dates from the earliest epoch of embryonic existence, while its normal development is spread over an exceedingly large part, in fact the whole, of intra-uterine life. The complication and multiplicity of physiological functions united in this one organ may have something to do, also, with susceptibility to such disturbances of developmental timing or proportion.

The eye of lower vertebrates, as fishes and lizards, is very susceptible to experimentally controlled disturbances not only of mechanical conditions but of nutritional states. Stockard has shown that by merely interfering with the oxygenation of these embryos it is possible to produce, at will, a fused eye, a cyclopean eye or an anophthalmic monster, while the development and distribution of ocular pigment can be controlled and modified by similar agencies.

Data of experimental teratology show that peculiarities of temperature, chemical constitution, tonicity, and acidity of nutrient media and fluids may influence the energy and rate of development in normal ova and larval forms, causing an arrest, at a low stage, of definite cells or tissues and of organ anlagen, resulting on the one hand in the loss or non-appearance of certain parts or in the persistence of others which normally disappear. The various cleft formations of the eye or its component parts resulting in coloboma of lids, iris, or choroid, or nerve-sheaths are examples of the former, while persistence of the canal of Cloquet and of the central hyaloid artery in the vitreous, or of the pupillary membrane represent the latter type of anomaly. The Mongolian fold or epicanthus seen in dyscrinoid idiotism and in some cretins may also be a form of anomalous persistence of a structure which, like the third lid or the nictitating membrane of lower animals, may have embryonic anlage in man which normally, and usually, retrogresses in fetal life.

The association of marked developmental defects, amounting even to microphthalmos or anophthalmos, with a rudimentary state of the brain does not necessarily indicate a causal relation. Both conditions may well be coincidental expressions of a common underlying factor. That the normal growth of the eye does not depend on brain development is shown, further, by the fact that normal eyes are often found in anencephalic monsters or in those in which failure of the lateral vesicles to develop normally resulted in a cyclopic brain or nose.

The influence of the individual glands of internal secretion, on processes of heredity are not fully understood, nor is it known whether definite dyscrinisms are transmitted in the germ-plasma and chromosomes, so that it is not possible to refer this or that ocular malformation or developmental arrest to one or the other endocrin organ. The relation of the endocrin hereditary factors becomes interesting and suggestive in ophthalmology because of morphological and clinical similarities and analogies between certain disease manifestations on the one hand and individual or racial characteristics of purely physiological significance, on the other. Thus the Mongolian fold or epicanthus, which is a normal heritage of the Chinese child and a stigma of marked constitutional degeneration in a Caucasian, is in both an evident endocrin marking which it is logical to assume is of uniform provenience. Congenital cataracts are frequently of the lamellar form noted as a regular accompaniment of certain definite states of dyscrinism and malnutrition, notably disturbance of calcium metabolism, such as rickets, tetany, and pellagra. Congenital keratomalacia is almost exactly paralleled by the corneal degeneration seen in animals deprived of the fat-soluble vitamin. Hereditary pigment degeneration of the retina is marked by hemeralopia which is an invariable accompaniment of a series of acquired starvation states, general or specific. Finally, certain congenital ocular dystrophies are associated with somatic

changes which point definitely and directly to the underlying disturbance, that of calcium metabolism again in the case of congenital fragilitas ossium with blue sclerae, or of similar states with corneal abiotrophies such as buphthalmos or keratoconus.

Cataract.—*The Lens.*—This ectodermal structure responds like others of its kin (skin, nails, teeth, hair) to various disturbances of nutrition, especially to deficiency diseases and dyscrinisms. The influence of nutritive disturbances in the causation of developmental defects is suggested by the experimental production of cataract in the young by sensitizing pregnant rabbits with lens tissue.

In chronic tetany there is an early development of cataract, always bilateral, of a peculiar type. It is perinuclear and lamellar (Barker). This would indicate a nutritive disturbance with intermissions, pointing to continued spastic contraction of the nutrient vessels in iris, ciliary body and choroid. The nucleus, being furthest from the capsule from which osmotic nutrition takes place, suffers most. There is an analogy here with the selective disturbances in the extremities in such grave vascular, nutritional diseases as thrombophlebitis obliterans, and perhaps, pellagra, in which cataract has also been observed.

The teeth defects, transverse furrows, holes, or parallel horizontal grooves (Barker) especially in canines and incisors, in tetany, are, similarly nutritional disturbances at the peripheral point of least resistance, or, rather, least nutrition.

It seems logical to attribute the lens changes to a spasmophilia involving the arteries of the uveal tract. The underlying biochemical process is explained by Verhoeff as a persistence of lipoid droplets normally present in the fetal lens due to a faulty fat metabolism dependent on or associated with disturbances of calcium metabolism.

Changes in the epithelium of the ciliary body, and swelling with hydropic degeneration of the pigment layer of the posterior surface of the iris in cataract of tetany and that of pregnancy further support this view. The deficiency cataracts of childhood are generally lamellar, partial, and stationary, and may interfere only slightly with vision.

In adults the lens changes are more usually nuclear, and tend to progress rapidly, with a decided hardening of the nucleus and the final development of a completely opaque lens.

Senile Cataract.—Like the skin, the lens shows, exquisitely, the onset of old age, and like the blanching of the hair, it is, one may say, a physiological change. However, just as we may have a pre-senility due to dyscrinism which shows itself in skin changes (geroderma) so an early development of arcus senilis, or of lenticular opacities, or diffuse cataract may indicate a gradual loss of the hormones which preserve youth.

The significance of arterial supply for the nutrition of the lens is suggested by the development of so-called heterochromic cataract or unilateral

complete opacification of the lens in connection with grave degenerative forms of cyclitis and of iritis involving a loss or change of color in that membrane.

Dryness of the skin, brittleness of the nails, and baldness, combining to form a syndrome of ectodermal pre-senility are dramatically checked by the administration of thyroid extract (Starr) and the action of the iodides, internally or in the form of subconjunctival injections in senile cataract are suggestive in this connection.

Corneal Changes in Senility.—*Arcus senilis, gerontoxon.*—The appearance of a gray crescent or semicircle just within the clear cornea near the limbus was from the earliest times associated with baldness or white hair as a sign of aging.

The influence of endocrin factors is indicated by the varying age incidence of these conditions in healthy individuals, by comparatively early onset after continued disturbances of nutrition, and by their sudden appearance in exceptional but undoubtedly genuine, cases immediately after severe emotional shock. It is a question whether the highly pigmented eyes and hair of brunettes indicate a type which tends to premature grayness. The latter, like precocious development, is generally attributed to thyroid influence, and might be explained on the basis of a relative hyperthyroidism setting in with an all too early gonad deficiency.

Ocular Pigment.—The biologic significance of pigment is by no means simple or completely understood. There are indications that it is in some way connected with all sources and manifestations of energy, cosmic as well as vital. Sunlight and heat are the primal sources of all energy and of all pigment (cf. coal, carbon, chlorophyll, hematin, and skin-pigment), and the coloring matter in the human economy is related to and probably derived from iron (hemosiderin). Ocular pigment, uveal as well as retinal, is a melanin derived from the pigment of the blood or, more probably, from protein chromogen.

The biological relation of light and in fact of all radiant energy to pigment in organic life is indicated by phototropism and heliotropism not only of organisms in lower life but of all plant and animal cells. Phototaxis acts on all protoplasma, only part of which becomes differentiated to light sensory cells. Light of high intensity affects not only the visual cells but all ectodermal elements as shown in dermatitis, sunburn and freckles and in the therapeutic effect on epithelial neoplasms.

Photochemical reactions in the retina associated with pigment are not thoroughly understood or uniformly interpreted. Visual purple is a product of an acid metabolic reaction and decolorizes phenolphthalein (Putter). Its action is probably a sensitizing one on the visual cells which themselves have a secretory function. The actual chemistry of the visual process may be explained as simple splitting, analogous to the decomposition by light of hydriodic acid; as a more complicated process of alternat-

ing as- and dissociation, or as a change in photo-electric conductivity resulting in greater or less sensitization of the essential cells to light, as in the case of selenium. It is significant that the completely pigmentless eyes, as of lumbricoids, are structurally adapted for vision in the dark only, while the eye in retinitis pigmentosa can see only in bright daylight.

Pigment plays an important part in the histology of the ocular tissues, notably that of the uveal tract (choroid, ciliary body, iris) as well as in the functional reaction of the retina to light and color which is itself a pigment dissociation in the terminal nervous elements of the perceptive layer (rods and cones). The relation of pigment to visual processes is indicated, clinically, by the incidence of marked irregularity of pigment distribution and massing in the choroid and retina in various forms of hereditary eye disease of which retinitis pigmentosa is the type and hemeralopia a prominent symptom. The opposite condition of pigmentary defect, or albinism, is characterized, similarly by defective vision associated with ocular unrest due to nystagmus.

The term, pigment atrophy, so frequently used seems to me inaccurate. There is reason to believe that body pigment derived from the blood as a constituent of tissues is never destroyed, however much interned, transported, or rearranged under the influence of radiant energy, heat, or inflammation, as in freckles, xanthelasma, or choroiditic deposits.

The relation of biologic pigment to vital energy is suggested by the difference in resistance to disease and exertion of blondes and brunettes. The development of pigment seems to depend on and be related to hair growth and secondary sexual characteristics, and like them to be under the control of the adrenal, medulla or cortex.

Ocular Pigment and Race. From the earliest times color was looked upon as the determining factor in differentiating human species, and we distinguished black, brown, red, yellow, and white races. Color referred pre-eminently to the skin, iris, and hair, and blonde meant generally blue-eyed. The endocrin implications of ocular pigmentation have not been worked out. My own experience is that the blue iris, which is essentially an iris lacking in stroma pigment, is found more often in races and individuals with a marked thyroidal dominance, that is, in Nordics and in sympathetic-tonics. It is also more common in myopia which may be considered as an overdeveloped eye with a tendency to excess metabolism and chorioretinal affections involving pigment loss or redistribution. The dark iris of the Mediterranean and other brunette races associates more often with a small pupil, round i. e., hypermetropic eye, and relative vagotonia. It is generally accepted by most observers that there is little or no stroma pigment in the iris at birth when it appears gray, blue or slaty gray by translucence of the uveal pigment on the posterior surface. Entrance of pigment granules into the stroma in the course of early childhood produces various tones from hazel to brown

or the dark-brown which is usually reckoned as black. There is a marked difference in individual irides in the distribution and arrangement of the pigment granules, some irides appearing of an even tone and others showing a marked speckling, usually of a lighter color than the even background. This too is a fruitful field for study, notably in lower animals and in birds who show the most brilliant and variegated pigmentation of the iris and of the tapetum.

Pigmentation of the iris, resulting in a brown eye, appears to be a dominant Mendelian characteristic. As this pigmentation associates with a relative vagotonia it gives color to the hypothesis that dominant characteristics are vagotonic and in some way connected with the hereditary transmission of pigment and energy. A crossed or double influence is noted in those cases in which we find a blue iris and dark hair as in certain Kelt-Iberians or the less frequent combination of brown eyes with flaxen head-growth (Germanic-Latin mixtures in Swabia and Bavaria).

The pigment of the lids is that of the common integument in general and shows, both in health and disease, the same reactions, which are largely endocrin. The disturbances in internal secretion which attend menstruation, pregnancy, the menopause, and senility are mirrored in pigment anomalies among which we may cite chloasma and the irregular pigmentations of gerontoderma, and xanthelasma. Xanthoma diabeticorum has almost a site of election in the soft skin of the lids, and xeroderma pigmentosum of heredito-specific origin often affects the conjunctiva as well as the lids. Histogenetically, the superficiay epithelium of the cornea is related to and must be reckoned with the lid-skin and conjunctiva which it parallels in its clinical manifestations.

The relation of pigment to hair is notable in the simultaneous occurrence of heavy brows, often tending to join, with dark irides and long heavy lashes. Pigment changes in ocular disease are most striking in the chorioretinal degenerations noted above, which depend on a specific heredity probably mediated by a developmental or nutritional dyscrinism which is quite analogous to the changes brought about by certain definite vitamin deficiencies.

Iris pigment may be so altered by chronic or relapsing inflammations as to cause a marked difference in coloring of two originally like eyes (heterochromia iridis) the degenerative nature of which is indicated by the frequent association, with cataractous changes in the lens. Migration of pigment from the iris into the tissues of the iris angle, the ligamentum pectinatum, and the neighborhood of Schlemm's canal have been noted both in glaucoma and in senile, otherwise normal eyes.

Anomalies of Ocular Pigmentation. Irregular distribution, deficiency or excess of ocular pigment is almost invariably associated with definite forms of visual deterioration and evidence of degenerative, rather than

inflammatory, processes in the light perceptive tissues of the choroid and retina. A familial and hereditary grouping is always recognizable. The symptom of hemeralopia which characterizes these affections as well as many forms of vitamin privation or deficiency disease has a relation to atypical pigment development, as well as to functional inferiority.

Lack of Ocular Pigment. Albinism. In this markedly familial and hereditary (Mendelian recessive) condition there is marked lack of pigment in the iris and uveal tract, and in the complete cases non-development of retinal pigment, as well. Nystagmus of the tremulous non-labyrinthine type is common. In both, vision is markedly impaired by irritation and dazzling, owing to the absence of a photostatic blind provided by the normal pigment layer at the back of the iris, intensified, in complete albinism, by a developmental arrest in the light-perceptive elements of the retina. According to Scherl, the first appearance of ocular pigment is connected with the development of the blood-vessels, so that defective pigmentation of the retina indicates an arrest at the earliest stage of embryonic existence, while albinism limited to the iris and choroid is explained by primary progress and a later standstill at the stage normally found in the newly born.

In albinism the lashes and brows are colorless or a very light blonde, not white as in senility. The hair is also extremely light and the skin thin and delicate. The visual disturbances range from rapid fatigability of the retina and sensitiveness to bright light with slight defect of central vision, to marked amblyopia, but always with a normal visual field and good color perception. The iris appears pink, lilac, or whitish-yellow, depending largely on the way in which light strikes the eye. The pupil reacts very briskly, is generally contracted and slightly rigid. Blepharospasm is a common symptom, as is the photophobia which it naturally follows. Hyperemia of the skin of the lids and of the ocular conjunctiva is generally present. Albinism is commonly but not at all invariably associated with psycho-neurotic inferiority and with developmental arrests.

Ocular Melanosis. Unusually deep pigmentation, especially of the sclera is found in the Negro race and in many individuals of dark complexion in Caucasian races. We speak of melanosis, in distinction to this marked but even distribution, when pigment spots or patches are found on an otherwise evenly and not excessively pigmented sclera, conjunctiva, or iris and choroid, or as an extreme rarity, on the optic disc. In the iris it appears as a distinct mass at the minor or major circle or at the sphincter margin or scattered over the surface of the iris in spots or lines which are generally irregular but often show a certain symmetrical arrangement in the two eyes.

Heterochromia. Occasionally, one half of the iris is light gray or blue while the other half is brown. Bilateral heterochromia (dikorus) is less

common. In neither case are other anomalies in structure or marking noted. The result of operations on these eyes shows that their internal organization is not normal (Hutchinson). In unilateral heterochromia, the lighter eye is the expression of an incomplete albinism and the developmental disturbance is accentuated by the general development of cataract.

Retinitis Pigmentosa. (Abiotrophy of the retinal neuro-epithelium.) This striking anomaly is generally accepted as a stigma of degeneracy. It is very frequently associated with congenital deaf-mutism. Heredity is a potent factor, and familial occurrence the rule. The factor of consanguinity seems to be of importance only in connection with heredity and environment (Shoemaker). Retinitis pigmentosa is not an inflammation, but a degeneration of the entire neurovascular tract of the peripheral portion of the end organ of vision, which probably extends centripetally well toward the brain. The primary tissue involved is the layer of rods and cones and the choroid, particularly the vessels, which are sclerosed and narrowed, while the smaller branches are often entirely filled and clogged by pigment masses which they carry into and deposit in the periphery of the retinal fundus in the form of fine masses like feathers, lace or bone-corpuscles. The disc is invariably waxy, dirty-looking, or white. There are no macular changes. Central vision is rarely interfered with. The field of vision shows marked concentric contraction with resultant telescopic vision as in looking through a tube.

At night and with lowered illumination sight is always very bad, (hemeralopia) owing to early degeneration of the paracentral region of the retina which is the most sensitive area to light in dark-adapted eyes. This interferes with freedom and rapidity of orientation and locomotion and causes the characteristic halting habitus of the subjects. In a certain class of cases, retinitis pigmentosa sine pigmento, only sclerosis of the choroid, retina, and vessels is found, with the usual degenerative atrophy of the disc, and the thread-like veins and arteries which are characteristic of the condition. Even in these originally unpigmented cases, however, deposits of pigment are found later on in the disease and may be just as marked as in the typical cases.

Cataract is a common accompaniment of retinitis pigmentosa, although in some cases it is a comparatively late development. The lens changes are usually found at or near the posterior pole with radially arranged or branching opacities in the deeper cortical layers. Doyne, and Knapp, note that extraction of these cataractous lenses gives unexpectedly good visual results.

[1] It would appear that pigment emigration follows the stimulus of light and is made possible or at least facilitated by vacuolization and other degenerative changes in the neuro-epithelial cells of the retina.

Ocular Physiology

But little is known of the endocrinological relations of the various functions and physiological processes in the eye or of the influence upon them of disorders of metabolism. Basic data are lacking in regard to the details of physiological nutrition in the various ocular tissues, particularly the retina under varying conditions of light stimulation and dark-adaptation. Similarly, the whole subject of intra-ocular tension as a resultant of two processes, ciliary secretion and ocular filtration, must be restudied from the standpoint of a science which will ask, for instance, whether there are different rates, either of secretion or of elimination, under varying conditions of body temperature, nutrition, endocrin balance, stimulation of vagus or sympathetic, to say nothing of the question of intra-ocular tension in Graves' disease, in obesity, in arteriosclerosis, or its relation to other tensions, vascular, respiratory, intracranial or intra-abdominal.

Pupillary reactions have been studied very carefully and traced to their cerebral, intracranial source. The various pupillomotor paths have been definitely mapped, but here again there is a lack of observations in health and disease of the special relation of pupillary reactions to organ stimulation, to emotional states, and to endocrin influence. The nerve control of the pupil by the vagus and sympathetic systems has been noted under various headings of this survey, and an attempt has been made to set up two types of ocular symtomatology, the vagotonic and the sympathetico-tonic, guided largely by pupillary manifestations. This division is suggested, as well, by a clinical determination of the influence of mechanical pressure on the eyeball, upon the rate of the heart beat, the Oculo-Cardiac Reflex of Dagnini-Aschner.

This reaction is elicited while the subject is at rest, after counting the pulse or the heart beat for one minute, by continuous fairly firm digital pressure on the closed eyes for the same length of time. The pulse rate is then again determined. Normally there is a slowing of three to five beats per minute, indicating the normal vagus tone. More decided slowing, an increased reflex, indicates vagotonia. Absence of slowing, absent reflex, or acceleration, inverted reflex, is indicative of sympathetico-tonia. There is no consensus as to the significance of this reaction, as yet. Numerous factors such as ocular tension, refraction, age, and the coincident effect of mydriatics or meiotics must be taken into consideration in health, while the observations in disease, systemic as well as ocular, are by no means adequate or uniform.

Winking and Tear Secretion.—Both these physiological processes are under a double vegetative nerve control which presents striking implications for function and pathology. There is in both cases a double func-

tion, on the one hand a constant more or less automatic action for local purposes of protecting the retina from the effect of bright light and the conjunctiva and exposed portions of the globe, particularly the cornea from drying and from the irritating action of dust and small foreign bodies, in which the tear secretion acts as a miniature irrigation and the wink (Lid-schlag) or sweep of the lid as a mechanical cleansing or mop.

There is reason to believe that this manifestation of the function is under vagus control, as it responds to local sensory impressions via the trigeminus and is increased by local irritation, as in conjunctivitis or the presence of a foreign body within the lids or by irritation of the mucous membrane of the nose. Lachrymation and clonic blepharospasm are common symptoms in all superficial ocular inflammations and injuries. Both lachrymation and the reflex lid sweep are diminished or abolished when the sensibility of the surface of the eye is diminished or abolished either by disease or drugs (glaucoma, cocain), and conversely, the cornea becomes hyp-or anesthetic in affections attended by paralysis of the lid (paralytic lagophthalmos, neuroparalytic keratitis). The physiologic rate of winking and of tear secretion under like conditions and varying vagus or sympathetic tone or with varying endocrin dominance would be an important and possibly instructive subject for clinical and experimental study. The sympathetic control of winking and tear secretion is shown most strikingly in crying under the influence of emotion. The biological mechanism and the purposive, phylogenetic development of this reaction are not known.

Tonic contraction of the orbicularis, causing a partial closure of the lid-fissure, is part of the mechanism of a defensive intensification or accentuation of fixation, as is noted in peering or screwing up the lids in the attempt to hold the eye on an object of interest and to get the sharpest possible vision by concentration of the gaze. There is no question here of an optical effect by the production of a stenopeic slit, as might be assumed, for the reason that the lids do not encroach on the visually concerned central area of the pupil. Quite the same reflex is noted as a protection of the globe against sudden strain on the ocular vessels and against mechanical protrusion in sudden rise of intra-abdominal pressure as in straining at stool, lifting a heavy weight, vomiting, or the expulsion of the fetus; in obstructed expiration, as in sneezing, coughing, laughing.[1]

Rider has shown that there is a uniform tendency to wink with the functionally, visually weaker eye.

Alteration of tear secretion has been noted in various dyscrinisms as mentioned above (v. hyperthyroidism). Infrequent winking is noted in extreme fatigue, in terminal stages of wasting disease, and after instillation of cocain, adrenalin, and atropin. In the case of the two latter

[1] With tonic contraction of the brows, the pupil, and the jaws, this narrowing of the lids is seen in all offensive-defensive reactions of the organism, and is the char-

there can be no question of the coöperation, as a factor, of lowered sensibility of the surface of the eye. These mydriatic alkaloids also, it will be noted, check the secretion of tears.

Ocular Motility. The rate of motion of the eyes in associated action varies with the direction. Motion inward is most rapid; next, motion upward. There is probably an individual, personal, speed or gait and possibly racial peculiarities. The slow movements of the eyes in narcotic states, in fever, and in the exhaustion of wasting disease are quite in keeping with the action of the lids in the states noted above.[1]

Excess convergence is frequently seen in hyperopia with eye-strain symptoms and might be considered as a spasmophilic manifestation or habit. Convergence defect or insufficiency of the internal recti muscles is seen in myopia, often in connection with subnormal accommodation, as a sympathetico-tonic or vagoparetic phenomenon in hyperthyroidism.

Intra-Ocular Tension in Relation to Nutrition and Secretion.—The relative softness or hardness of the globe depends partly on the rigidity of the sclera and partly on the relation between intra-ocular secretion and elimination via the filtration angle of the anterior chamber. The individual differences in tension depending on age, refraction form, complexion, or possibly endocrin dominance, have not been studied. Reduction of tension after slight contusions of the globe associated with enophthalmus and a contracted pupil suggest a connection of hypotony with vagus irritation or an equivalent sympathetic paralysis. This is corroborated by the incidence of lowered tension with neuroparalytic keratitis and other forms associated with anesthesia of the cornea and evidence of lowered trophic nerve influence.

Increased intra-ocular tension, on the other hand, has been observed in attacks of herpes zoster. Weeks reported a case, and reviewed three others, of acute glaucoma on the same basis. Increased specific gravity of the aqueous and diminished filtrability owing to the presence of albumin, globulins, and possibly other products of inflammation, have been accused as the pathogenetic factor of hypertension in these cases. This view is very theoretical, based on insufficient evidence, and, it seems to me, directly contradicted by the infrequency of high tension in other inflammations attended with similar chemical changes in the intra-ocular fluids. We must look, rather, for the responsible disturbance of vegetative nerve

acteristic feature of the fighting face. Habit makes of this ocular gesture an expression seen in the eye of the commander. Relaxation of vagus tone gives us the large pupil, wide lid-fissure and detached, non-fixing, dreamy gaze of such emotional states as love, revery, or ecstasy, and the eye of the poet and dreamer.

[1] Large objects move slowly and large persons (pituitary) are often strikingly slow and "heavy footed." Whether this is a result of mere bulk or part of the physiological endocrin dominance is an interesting question. Compare with this the chipper, bird-like motions, the quick, brisk glance of the restless, eager, inquisitive, and impulsive thyroid type.

control in the eye, due either to infection or to pathological inflammatory change, as in herpes, in the nerve itself.

Hypotony or loss of tension is generally a serious symptom pointing to progressive loss of vitality and deterioration of the eye. It is observed most frequently, if we disregard the purely mechanical hypotony of retinal detachment, in chronic or relapsing affections of the uveal tract.

Neuroparalytic keratitis, keratomalacia, and reticular keratitis are associated with hypotony.

Degenerative changes in the cornea, congenital or experimentally produced by feeding with devitaminized food, are generally associated with a decidedly reduced intra-ocular tension.

Herpetiform eruption, disturbances of sensibility with injuries or after alcohol injections of the Gasserian ganglion are often associated with marked increase in tension.

Malarial keratitis is, clinically, very similar to the above, suggesting at least a trophic disturbance, and this is borne out by the negligible effect of quinin on the corneal process. Endocrin treatment with adrenal and mixed glands should be beneficial.

Neuro-endocrin Control of Intra-Ocular Tension.—*Theory.*—Vagus control would involve a contracted pupil and uveal arteries and, ceteris paribus, a lowered or at least not increased tonus. Narrowing of the pupil by meiotics does not cause increased tension in normal eyes. Sympatheticotonia would provide a more active secretion of aqueous, and by dilatation of pupil and rolling up of the filtering area conduce mechanically to a diminution of drainage, and consequent rise in tension.

Clinical. Ocular tonus, the relation between secretion and elimination, probably depends on a double control, vagotonic and sympatheticotonic. The former undoubtedly tends to lower tension, the latter to raise it. However this may be under physiological conditions, clinical observations in acute glaucoma undoubtedly indicate a marked sympathetic irritation as one, at least, of the causal factors, while the symptoms are in accord with this view, and the beneficial or curative drugs and procedures are, without exception, those which stimulate the vagus system or depress the already overstimulated sympathetic.

Predisposition to glaucoma was postulated for middle age or beyond, in hyperopes, by a theory which laid stress on the mechanical factors of a shallow anterior chamber, large lens, and, correspondingly small circumlental space, a narrow filtration angle, and a pupil which tended to dilate unduly under even a weak solution of a mydriatic. For this reason it was that oculists feared instillations of atropin, say for refraction tests, or even its internal administration in older patients.

Provocative instillations of cocain were used to determine the above-mentioned susceptibility to mydriatics which indicated a predisposition to glaucoma.

How can we reconcile these observations with the known facts that the pupil in and after middle age tends to be small and somewhat spastic, especially in hyperopes, and that under these circumstances there is rather a resistance than a susceptibility to atropin?

The clue is given, I am convinced, by the factor of acute paralysis of vagus activation under the influence of emotion, fatigue, cold, or other vago-depressing agencies. When such factors act on a structurally predisposed eye, as described above, the outcome is apt to be an acute attack of glaucoma. Given the opposite type of eye, i. e., an eye with myopic build, large pupil, deep anterior chamber, and roomy circumlental space with a rather thin and non-rigid sclera already established by the axial elongation, and the endocrin storm may well pass over without a sudden rise in intra-ocular tension. Here, the ocular symptoms are those of sympathetic irritation, and when the attacks are repeated often we may have all the appearances of Graves' disease.

Glaucoma and exophthalmic goiter would on this supposition be mutually exclusive, to a degree, if not completely. Or, otherwise expressed, the emotional and other stresses which deplete the vagotonic system, particularly excessive sympathetic irritation via thyroid irritation, produce either an acute attack of glaucoma or a tendency to exophthalmic goiter, according to whether the eye is hyperopic and vagotonic, or, on the other hand, myopic and sympathetico-tonic. v. Hippel found evidence of thymus, as well as of thyroid, hyperplasia in his cases of glaucoma.

Glaucoma.—Theories of causation of pathologically increased intra-ocular tension are as leaves in Valombrosa, or as cures for hay-fever. Through all the hypotheses there has run, however, the red thread of a possible neurotic factor. The purely mechanical theory of predisposing topographic relations, of the combination of a large lens, flat anterior chamber, hyperopic refraction, was superseded or rather completed by the idea of an edema of the vitreous, a conception taken over almost wholly from colloidal chemistry.

Hamburger's theory assumes that the entire iris acts as a sponge in contact with anterior chamber and that this tissue is of paramount importance for fluid exchange, while the canal of Schlemm, despite Leber, is of little value. Paralysis of the pupil and lowered sensibility of the cornea are explained by the influence of the central (? vegetative) nervous system. Racial predisposition of Jews shows nervous (?) factor.

Etiology. Emotional stress, worry, fatigue, cold, thyroid depletion by climacteric changes, and chronic infections.

Glaucoma is almost without exception an affection of later middle life coinciding with the menopause and the male climacteric. Emotional disturbances, especially those like prolonged worry from business troubles or ill health which deplete the endocrin (adrenal) reserve, are important factors, as are repeated exposure to cold and fatigue. The

marked predisposition of Jews to this affection is significant in view of the emotional history of the race, the prevalence of neuroses (speech-defects, neurasthenia) and of metabolic disorders (diabetes, arthritism) of endocrin origin, or the sudden development of acute glaucoma "under the bandage" after operation (iridectomy) on the fellow eye.

Pathology. There are certain discrepancies in the theories which lay stress on mechanico-physical factors. Hypermetropia is most common in youthful eyes, yet at this age glaucoma is not only uncommon, it is almost unknown. Intra-ocular tumors (glioma, sarcoma of the choroid) may attain large dimensions without increasing intra-ocular tension or causing the dilatation of the pupil which was supposed to bring about the acute attack of glaucoma. It is a question whether increased intra-ocular tension alone is sufficient to paralyze the sphincter pupillae completely and whether there is not some other factor to be considered. It is to be noted that in some cases of increased tension where meiotics fail completely, the same alkaloids, administered in sufficient doses to produce systemic effects and the characteristic physiological reaction, promptly contract the pupil. This would speak against any terminal, mechanical paralysis sufficient to paralyze the nerve endings in the sphincter or the muscle fibers themselves.

Ocular agioneurotic edema associates with glaucoma logically as well as clinically and Barkan says that it seems too much to suppose, in view of the well recognized causes of certain classes and cases of glaucoma, that all these causes should only be favoring factors to the localized edema which raises the ocular tension. Are hyperopia, old age, stiffening of the sclerotic, relatively disproportionate increase of lens volume, fibrosis of the ligamentum pectinatum, high blood-pressure, arteriosclerosis, and sudden mental excitement, all only secondary to a local acidosis, or only an aid in its appearance in a type case of this kind? For acidosis is common in childhood; glaucoma, rare; there is no edema in diabetes, typically acidotic as it is. On the contrary, one finds hypotony in this non-edematous, highly acid state. Finally, the prompt action of meiotics in the case he reports, of angioneurotic intra-ocular edema with glaucoma, is hard to reconcile with the hydrophilic theory.

These considerations appear to me to lead directly back to an endocrin basis in the pathogenesis of glaucoma. The anatomic factors cited are all predisposing elements, as indeed we recognized before; acidosis is also a link in the chain, but a link merely.

Symptomatology. The constitutional disturbance is significant, especially the agonizing pain, radiating to a distance from the eye and involving the brow, cheek, and teeth; the severe headache, often associated with nausea; the marked prostration, exhaustion, and anxiety. Pain alone, however severe, in other eye affections never presents this picture, that of an endocrin storm; a picture which not infrequently misleads the

physician to a mistaken diagnosis of acute systemic disease or even of brain tumor.

The symptoms of acute glaucoma may be summed up as those of cervical sympathetic irritation, and the sudden incidence of an attack from a single instillation of a weak solution of atropin, from a sudden emotional stress, from exhaustion or exposure to cold, confirm this view. Per contra, the efficacious therapeutic agents are all such as stimulate the vagus system, and the operative procedure of removal of the superior cervical sympathetic ganglion is the only one which completely inhibits sympathetic irritation of the ocular functions.

Clinical and Therapeutic Implications.—The essentially anti-glaucomatous alkaloids, the meiotics, are pro tanto vagotonic. Elimination by heat, sweating, catharsis, as well as by the action of dionin, mercury, and the iodids are valuable therapeutic agents whose beneficial action has been determined empirically rather than scientifically. Of each and every one of these much of the effect is due to stimulation of one or other organ of internal secretion or to checking expenditure of valuable internal secretion. The action of iodin as a thyroid activator is particularly significant. Pilocarpin and eserin, besides contracting the pupil, and thus allowing the iris to develop to the full its action as a filter while freeing the iris-angle, markedly increase ocular secretion and metabolism generally. Morphin has the same pupillomotor action, and with heat and coffee, tends to allay pain and anxiety and thus restore resistance and cut down endocrin waste. The action of cathartics is likewise complex. The elimination of intestinal products of decomposition which furnish a source for toxins which are particularly deleterious to the thyroid and its immunizing function, is but one of these. The mechanical effect of mechanical depletion of the gut and of elimination of large amounts of fluid from the same area with the coincident derivative effect and the possibility of freer outflow of intra-ocular fluids must also be considered. The neutralization of an intestinal or even systemic acidosis by cathartics alone or assisted by alkalines or by the salicylates furnishes another factor. There is need for careful study of the chemistry of the vitreous and intra-ocular fluids in health and diseases to throw light on the question of varying acidity in different states of tension. Leeching and massage which are of undoubted value in glaucoma with severe pain act largely by mechanical action, but it is impossible to exclude a coincident direct action on the nerve-terminals in the iris and ciliary body tending to restore the normal secretory balance.

It is significant that meiotics are of the greatest usefulness and offer the most favorable outlook for a lasting therapeutic effect in cases of simple or non-inflammatory glaucoma, in which, it is fair to assume, the endocrin disturbance has not been complicated by marked anatomic or mechanical features leading to obstruction of the filtration angle of the

anterior chamber, and thus bringing on the acute inflammatory attack. In this connection we note the persistence of pathologically increased intra-ocular tension in spite of repeated iridectomies and the institution of various procedures, notably that of corneoscleral trephining by Elliot, all of which aim to establish a new and permanent filtration path from the interior of the eye to the subconjunctival tissue spaces via filtering or cystoid scars or actual fistulae.

Glaucoma may be considered from the endocrinological point of view as an exudative or hypersecretory disturbance due to sudden failure of vagus tone under sympathetic irritation and hyperthyroid activity (hyperhidrosis, tachycardia, susceptibility to adrenalin and atropin, and to provocative instillation of mydriatics), in hyperthyroid individuals and races, age (gonad deficiency and relative hyperthyroidism of the climacteric, male or female), and emotional state (endocrin exhaustion from worry, fright, cold, hunger, exhaustion, operation), and failure of immunity (chronic infections). The similarity to an angioneurotic edema on a basis of acidosis has been noted. The structural and anatomic features of the globe, depending partly on topographic relations determined by refraction (hyperopia), undoubtedly contribute in precipitating an acute attack, but it is by no means improbable that these very factors themselves may develop under endocrin dominance. The relation of ocular pigment to refraction type, scleral rigidity, and tonicity of the sphincter pupillae, and the combined effect of these factors on intra-ocular secretion and tonus in individuals of various ages and endocrin disposition form an interesting subject for clinical and experimental investigation.

Encyclopedias and systems of medical ophthalmology treat of the etiological relations of ocular disease to affections of the organism as a whole or of individual systems such as the respiratory, the intestinal tract, the cardiovascular or the nervous system, and in addition enumerate and analyze the ophthalmic signs and symptoms which are of diagnostic value in the interpretation of general morbid conditions and may be characterized as systems of ocular semeiotics of constitutional disease. A certain amount of repetition is inevitable, depending on the correlation and interplay in many cases of two or more systems with the ocular manifestations, such as nervous system and digestive tract, genito-urinary and vascular tract, and so on. From the standpoint of endocrinology and pathology of metabolism it would be expedient to modify the arrangement and classification of our clinical material and consider less the anatomic or systematic grouping of the organs than their relations to more basic nutritional and developmental factors in health and disease. This applies not only to local affections of the various organ systems but to the border line conditions in developmental disturbances, the biological variations of sexual and developmental periods or epochs, and even to infections.

The term idiopathic applied to disease forms has always been a confesssion of ignorance, a reproach as well as a testimonium paupertatis in etiological knowledge. Inherent in the word, however, was the connotation of idiosyncrasy, of a heightened susceptibility or disposition to certain disease forms depending on a diathesis which might be inherited, congenital, i. e., communicated in fetal life, or genuinely acquired. The essential character of many if not all diatheses as deficiencies of one or other essential element or better, end-product, of metabolism is now generally recognized. Such deficiencies may be brought about in various ways as by disturbances in the succession or quality of individual metabolic reactions, resulting in a faulty biochemism, by a predominance of one or other dietary component to the extent of causing intolerance, or, again, by a lack of certain food forms or, more important still, of one or more of the essential vitamins. The hormones are in some respects analogous to the vitamins. These vitamins which have hitherto been isolated and studied relate to the prevention of scurvy, of multiple neuritis, and of rachitis, respectively. Hess has shown that there are certain marked analogies between the clinical manifestations of scurvy and those of exophthalmic goiters, while Pfaundler and others accentuate the similarity in manifestations and pathogenesis, of exudative diathesis, lymphatism, and arthritis.

The suggestion arises that the complex metabolic processes and reactions of the organism may be, in the last analysis, dependent on much simpler factors, such as physiological plus or minus of acid or alkali in tissues and secretions.

This view would endow vitamins as well as hormones with the eminent faculty of controlling the acid-alkaline balance. It is significant that so many of the symptoms both of vitamin deficiency and of dyscrinism are associated with manifestation in their end states of an excess of acid or of lack of calcium. Cyclical vomiting, gastro-intestinal irritation, asthma, migraine, angioneurotic edema, and not at all improbably, glaucoma, are from the endocrinological standpoint, spasmophile reactions affecting definite regions, or, more properly, organ systems and tissue categories. This spasmophilia is, one might say, a normal expression of vagotonia, and the latter is invariably the index, of an acid state or dyscrasia, inherited or acquired and mainly controlled by the vegetative nervous system.

It seems fair to assume that chemical allergy via foreign protein sensitization may be a factor, and in some cases a passive, endogenous, sensitization through excess or defect of essential endocrin activators of metabolism. Thus, asthma from ingestion of egg albumen; the association of tonsillar and adenoid hypertrophy with hypoplasia of the systemic lymph-glands and acidotic indications of disordered parenteral digestion

of fat; drug eruptions and conjunctivitis and dermatitis of the lids in atropin idiosyncrasy.

Ocular affections and Eye Symptoms in Disorders of Metabolism. With an abnormal chemical constitution of the blood as a direct or indirect result of disordered metabolism, changes are found in the ocular tissues which are quite similar to those observed in other parts of the body and which are of importance first on account of the accessibility of the eye to minute clinical examination which gives it diagnostic importance in general disease, and further because of the prognostic and functional significance of even slight disturbances of circulation, to say nothing of severer accidents such as hemorrhages in the light-perceptive tissues (choroid, retina) or into the transparent media.

Ocular hemorrhages into the conjunctiva or deep seated extravasations in retina or vitreous are not uncommon in the various forms of anemia and profuse hemorrhages in other organs (uterus, stomach) and are not infrequently followed by retinal or neuroretinal inflammation or optic atrophy.

Similar disturbances are frequent in pernicious anemia and in leukemia with multiple hemorrhages or actual retinitis. In various metabolic disorders attended by entrance, into the blood, of pigment or other constituents of the bile, icteric discoloration of scleral conjunctiva is a striking symptom. This is the more easily detected as the underlying sclera is of about equal whiteness in blondes and brunettes, so that the yellowish discoloration appears in the eyes much sooner and in slighter degrees than in the skin or mucous membranes. Here, too, hemorrhages are not infrequent, especially in the retina, vitreous, and anterior chamber. The pus of a coincident conjunctivitis (gonorrhea, purulent catarrh) is often distinctly icteric but the tears are never stained in this way.

In this connection we may refer to transitory myopia due to an increased refraction of the aqueous, similar to that observed in diabetes and Bright's disease, owing to the presence of biliary products and possibly albumin. Xanthopsia in chronic hepatic disease has been attributed to icteric discoloration of the vitreous.

Ophthalmia Hepatica. Under this heading, an ocular complication of chronic disease of the liver and biliary passages has been described which is marked by typical hemeralopia and disturbances of vision due to pigment epithelial changes in the choroid and retina similar to those described in chorioretinitis pigmentosa (q. v.). Concentric contraction of the field is commonly, and blue blindness occasionally, seen. Epithelial xerosis of the conjunctiva and cornea and keratomalacia, again with the typical hemeralopia, have been noted in these cases, and as an expression of nutritional disturbances in the eye due to a lack of bile or to the presence of bile by-products which like bile acids are known to dissolve the visual purple. Observations on this subject date back to the earliest

times, and the Papyros Ebers contains a description of the disease with the advice to have the patients remain in a dark room and be fed with ox liver.

Hemeralopia with degenerative processes in the conjunctiva and cornea have been noted in purely qualitative deficiencies of diet as in prisons, after long fasts (Russia) as an expression of vitamin deficiency quite analogous to that produced experimentally in animals by withdrawal of the fat soluble vitamin and relieved promptly by the administration of cod liver oil. A connection with calcium metabolism is evident, but the details have not been worked out.

Intoxication and the poisoning by the toxins of spoilt sausage (B. botulinus), olives, and other canned but not properly preserved foods also acts on the eye in the manner of belladonna poisoning, producing paresis or paralysis of pupillary action and accommodation, with blurring of vision due to these disturbances, but no optic nerve or retinal affection.

Gastro-Intestinal Auto-intoxication was at one time as much overworked as an etiological agent in visual disturbances as, according to Barker, it was in hypertension of the arteries. To paraphrase his advice, certainly, if chronic constipation or other disorders of the digestive tract be found in patients with eye affections, corrective measures should be instituted. In chronic uveitis, good results have attended the cleansing of the lower intestinal tract by high colonic irrigations followed by an alkalinization where the bowel contents were markedly acid and the implantation of colonies of B. bulgaricus or B. colonis according to the bacterial needs of the intestine as determined by culture tests, as suggested by Dwyer and others. The same dietetic and hygienic therapeutic measures might well be employed in optic nerve disease with obscure etiology and evident disturbance of intestinal digestion.

Intestinal parasites may cause ocular symptoms as a result of irritation alone or by the entrance into the interior of the eye of their embryos (cysticercus, echinococcus) or, more rarely, as in the case of bothriocephalus, by toxic worm products entering the circulation and causing ocular paralysis or inflammation.

Trichinosis finds local expression in symmetrical edema of the fornix fold, lids, and conjunctiva, which probably also affects the orbit as shown by the usual accompaniment of slight exophthalmos. Marked hyperemia and capillary conjunctival hemorrhages have also been noted. Paralyses of the external ocular muscles, due to invasion by the parasite, are comparatively rare, while mydriasis and loss of accommodation are more frequent. As trichina does not invade unstriped muscles, this must be explained by toxic action, the nature of which has not been definitely determined.

When abdominal plethora was a favored expression, the asthenopia often noted in obese and sedentary gluttons was attributed to this rather

vague condition, and restriction of diet, active exercise, and the waters of Carlsbad, Bath, and other spas, formed a favorite and effective form of treatment. To-day, physiological chemistry would no doubt give a more precise definition of the metabolic disorder, but the treatment would be along the same general lines.

Intestinal stasis and putrefaction of fecal matter in a congenitally dilated colon (Hirschsprung's disease) was noted by Schoenberg in a child of four with acute retrobulbar neuritis which promptly cleared up under evacuation of the bowel and colonic irrigations.

A. Knapp reports a number of cases of sympathetic uveitis in which the intestinal autotoxic factor was indicated by the history of improper diet, overfeeding and constipation. The usual treatment by mercurial injections, sodium salicylate, pilocarpin sweats, did not seem to have very much effect, but the condition improved rapidly under restricted diet and the Dwyer procedure for regulating the chemical metabolism and bacterial flora of the lower intestinal tract.

In line with these observations we may mention the report of relapsing uveitis and sympathetic ophthalmia cured or greatly improved by parasepecific protein sensitization by the injection of Coley's toxins (Verhoeff) or a combination of typhoid, vaccine and autogenous vaccines (Wiener-Bonime).

Keratitis, uveitis, and retinal hemorrhages have been seen often after antityphoid inoculation, which de Lapersonne claims is particularly dangerous to arthritics, syphilitics, tuberculous, over forty years of age.

Focal infections, of the teeth, tonsils, intestines in children, of teeth, gall-bladder, appendix, later; in old age, of sinuses, and prostate, are common sources of toxemias which generally affect the uveal tract and, occasionally, the retina. Arteriosclerosis and chronic hypertension are often due to chronic focal infections and to rheumatism (Ophuels), with final grave depression of adrenals, thyroid, and sympathetic, with vagotonic ocular symptoms and tendency to glaucoma. Pre-senility, constipation, irascibility, high blood pressure and vascular sclerotic changes in choroid and in iris-angle (Fridenberg) predispose to increased intraocular tension.

Teeth. Functional disturbances such as strabismus, ptosis (Hancock) or reflex ocular neuroses, expressed as asthenopia, accommodative anomalies, complete and partial paralyses, heterophorias, spasm of the orbicularis, with neuralgia, and sensitiveness to light, may be caused on a basis of sympathetic irritation of the exposed vital pulp of a tooth through heat or cold or by direct contact with foreign substances. Uveal disease, especially septic exudative chorioiditis, is often due to apical or alveolar abscesses of chronic type, and toxic absorption is the all important factor. Metastasis has never been observed. Rowe claims that dental infections are the commonest cause of both functional disorders and true

inflammatory changes in the eye and that general toxic absorption is shown by the frequent loss of weight and appetite, nervousness and inability to sleep.

Pellagra. Central scotoma for color and disturbances of the peripheral fields are early signs of this affection, and in advanced cases pallor of the optic nerve heads is found (Calhoun).

Constitutional Disease and Endocrin Disturbances. In the light of endocrinology and fuller knowledge of certain clinical conditions we shall have to revise, at least in part, our conceptions of etiology and pathological mechanism connected with rheumatism, and possibly with syphilis and tuberculosis.

Rheumatism and Arthritic States. Pemberton concludes on an intensive study of four hundred cases that indiscriminate removal of teeth has gone too far, that with chronicity the results of the removal of pus foci become less important, and "in a regrettable number of chronic cases and in some early instances, the removal of focal infection may be of no avail whatever." He lays stress on the etiological significance of exposure to cold and wet, and to diffuse infections—as opposed to foci—such as dysentery, influenza, and pneumonia, while quiescent foci may be made operative by a severe illness and reactions following endocrin alteration by emotional stress. The beneficial effects of radium, the roentgen ray, arsenic and massage indicate, as does the improvement under thyroid administration, that agents which hasten body metabolism have a good effect on arthritis. Arthritics show a lowered elimination, and a lowering of sugar tolerance which, in turn, seems to be markedly dependent on focal infections and their removal. In many cases, however, this lowered sugar tolerance remained in spite of removal, or returned to normal in spite of persistence of pus foci, with cure by other means. Cutting down food, particularly carbohydrate intake, and stimulating metabolism by heat and hyperemia are valuable procedures. The starvation preceding and following narcosis and operation has a great deal to do with the beneficial effects of adenectomy and tonsillectomy usually ascribed to surgical intervention in chronic arthritis, and may explain in part the not infrequent relapses, of which Pemberton cites a number, when these patients were again placed on full diet. The application of these clinical studies to the management of rheumatic eye affections is evident, particularly in iritis and the ocular manifestations of gout, such as the various forms of scleritis and the hot eye of keratitis. At first, salicylates, then removal of focal infections and intestinal débris, and now, stimulation of basal metabolism via endocrin medication. The frequency of myositis in Pemberton's series suggests the possibility, in inflammatory affections of the extrinsic ocular muscles and possibly in the sphincter iridis and muscle of accommodation, of a more frequent agency in the form of lowered metabolism dependent on a generally hypothyroid dyscrinism.

I refer again in this connection to the incidence of constipation and resulting intestinal toxemia with hypothyroidism.

Treatment of ocular rheumatism. Protection from cold and changes of temperature, sharp limitation of food, removal of foci, arsenic, iodids, hydrotherapy, massage. Above all, hot compresses, leeching, dionin, atropin, catharsis, systemic alkalinization, thyroid activation.

Diabetes. In this grave disturbance of metabolism, various ocular affections are encountered. The commonest are disturbances of refraction and accommodation, opacities of the lens and vitreous, intra-ocular or retinal hemorrhages, and less frequently optic neuritis and atrophy.

Paresis of accommodation is noted in cases of long standing, and seems to depend as much on general debility as on the altered chemism of the blood. A change of refraction in the direction of hyperopia or diminished myopia is probably due to actual sugar content of the lens and other refractive media (vitreous) and fluids. That there is any actual axial change or decrease in the volume and contents of the globe is rendered highly improbable by the rapid variations in the refraction total, the restoration to normal conditions when the sugar content of the blood was reduced, and by chemical analysis of the lens and intra-ocular fluids which showed the actual presence of sugar (Leber, Knapp, Becker).

Diabetic Cataract. This condition has been ascribed to general debility, loss of intra-ocular fluid by dehydration, and, again, to the actual presence of sugar in the fluids of the eye. The changes are generally nuclear, and not infrequently unilateral. The bilateral, less common form, is a uniform clouding of the more superficial cortical layers and has been seen to retrogress, all of which would indicate a dependence on chemical changes in the fluids which are in immediate contact with the lens capsule.

Retinal disturbances occur mainly in cases of long standing diabetes. Hemorrhages and retinitis are seen. The latter shows less extensive exudation than the form due to nephritis, while the blood effusions are often massive. It is generally considered prognostically grave. Ocular palsies affecting the lids and the extrinsic ocular muscles, either single or combined, are not unusual in diabetes. They are frequently transitory. Marked hypotony has been observed in diabetic coma by Riesman and others.

Albuminuria and Renal Disease. Edema of the lids is a common symptom of various forms of nephritis, particularly those associated with subcutaneous edema, anasarca, and dropsies. The lower lid shows a certain predilection by reason of the laxity of its subcutaneous cellular tissue and the factor of gravity and is early affected by edemas which are often evanescent or relapsing. In cases of persistent albuminuria, loss of accommodative action is not uncommon.

Retinal hemorrhages and actual exudative inflammation (Bright's

neuroretinitis) are, as is well known, common in advanced nephritis and usually of unfavorable prognostic significance. The retinal changes are fatty degeneration, hemorrhages with changes in the smaller vessels, and edema. Papilledema is the usual form of the optic-nerve manifestation. Complete blindness without ophthalmoscopic changes, uremic amaurosis, is seen at times with convulsions, vomiting, and coma indicating a grave general disturbance. The rapid appearance and disappearance of this condition indicate that it depends on retention of urea in the blood rather than on the factor of increased intracranial pressure secondary to edema which is the probable cause of papilledema in Bright's disease.

Syphilis and Tuberculosis. The attenuated virus of lues and of tuberculosis transmitted to the offspring of the originally infected patient seems to have an actual selective action on the glands of internal secretion. Many and varied forms of nutritional and developmental disturbance and degenerative states may well be attributed to the dyscrinism rather than to any survival of the primary disease. In this connection we have in mind primarily the pigment degenerations of the retina and choroid with their characteristic disturbances of visual function. The striking symptom of hemeralopia or night-blindness, which is seen also in many deficiency diseases as a passing condition amenable to vitamin therapy, accentuates the probable correctness of this view.

Interstitial keratitis is seen in acquired as well as congenital syphilis, and in hereditary form as one of the Hutchinsonian triad of pegged teeth, deafness and keratitis. A clinically almost identical form of keratitis is seen in rickets and some forms of vitamin privation, and Risley and others have noted the good effect of thyroid extract in all forms of interstitial keratitis. In pigmentary chorioretinal disease, probably on a heredito-specific basis, Muncaster used mixed glands in conjunction with cacodylate of soda, with excellent effect.

The syphilitic inheritance seems to act largely by disturbing the normal functions of the endocrin glands and thus indirectly affecting immunity, nutrition, metabolism, and development. The diatheses such as rickets, lymphatism or exudative diathesis, or scrofula, all of which are marked by ocular diseases, suggest this origin as one at least of the factors.

Disorders of the Sexual Apparatus. Numerous affections of the eyes or of vision, particularly in females were formerly attributed to menstrual disturbances, ovarian or uterine disease, and so on. Various neuroses, especially hysteria, were traced to the same source and the ocular symptoms attributed to an underlying genital affection. The fact that even physiological processes connected with sex development, menstruation, pregnancy, and lactation, as well as the menopause and the male climacteric are closely connected with the internal secretion of the testes, ovary, placenta, and mammary glands, and that these profoundly influence

the endocrin balance, reduces to an almost negligible minimum the ocular affections which can be brought into a dependence on disease of the sexual apparatus *per se*. The hysterical manifestation, such as asthenopia, kopiopia hysterica, or accommodation spasm are largely expressions of an ocular vagotonia (q. v.) which is but part of the general spasmophilia indicated by globus hystericus, headaches, stomach cramps, constipation, acidosis, and so on.

Intoxications. Exogenous poisons, inorganic and organic, as well as poisonous products of disease processes and of disorders of metabolism have a marked effect on the visual functions. Many have a selective affinity for the optic nerve, notably lead, quinin, nicotin, morphin and some other alkaloids. The coincidence of pupillary contraction and of spasm of accommodation with general arterial contraction in the retina and nerve suggest, again, the factor of vagotonia. The mydriatic group, on the other hand, acts as a sympathetico-tonic or vago-depressant and the resulting symptoms are limited to the pupil and ciliary muscle while the function of the retina and nerve do not seem to be affected.

Ocular Morphology

The size of the eyeball as well as its axial proportions which very largely determine whether it is to be myopic or hypermetropic depend in great measure on the dimensions of the orbit and indirectly on those of the skull, particularly the area at the base in the neighborhood of the sella turcica. The ethnologic divisions of long-skulled and short-skulled races are paralleled by the categories, of more importance to the ophthalmologist, of chamai-conchs and hypsi-conchs (Stilling), according to the relatively high or low position of the pulley for the tendon of the superior oblique muscle on the inner (nasal) and upper aspect of the orbital cavity. According to Stilling, this mechanically determines the growth and proportions of the globe by directing the pressure upon it of the extrinsic ocular muscles during its pliable period of development in the act of fixation, especially in convergence. While this mechano-physical control may explain the relation of orbit to eye-form, there does not seem to be any corresponding theory to elucidate the variety (variation) in the development of characteristic, racial, skull-forms. The endocrin element, and above all the pituitary, is of prime importance. Apart from its influence on rhythm and tempo of growth, the mechanical proportions of this gland cannot be without influence on the dimensions of the sella and indirectly on those of the orbit, and a pituitary dominance within the bounds of the physiological will be indicated by typical ocular morphological features. Conversely, a deficiency of pituitary control will result in a type of eye which provisionally I shall describe as hyperthyroid.

The Thyroid Eye.—This type has a smaller, generally less massive orbit. As the skull form tends to dolichocephaly the orbital proportions favor the development of a long, axially myopic, eye. The lid-fissure tends to be wide and the pupil large, the ocular motions frequent, brisk, so that the glance is alert and the gaze concentrated, giving a sharp, wide-awake expression. There is decided vascularity of conjunctiva and lids, giving a full blooded appearance, and this condition, associated with a plenitude of orbital fat, causes a slight prominence of the eyes, a mild exophthalmos which merits and enjoys the name of pop eye, or as the French more poetically put it, les yeux a fleur de tête. Pigment is not abundant and may be deficient. Albinism is noted predominantly in this type which characterizes the blonde Nordic races, such as the Saxon and Scandinavian.

Winking is free, and lachrymal secretion active and reflex. Tonic contraction of the lids, blepharospasm, on the other hand, is infrequent. The vascularity of the superficial tissues of the eye is heightened to congestions with a tendency to catarrhal processes, conjunctivitis with secretion, or blepharitis with red lids. Ocular metabolism is raised and there seems to be a tendency to increased intra-ocular tension in sympathy with this plus of secretion. There is no tendency to headache, vertigo, spasm of accommodation or of convergence, associated or unilateral. The pupil reacts to relatively weak solutions of the mydriatics, dilating easily with cocain and at times with adrenalin, even in middle or early old, age, while comparatively concentrated solutions of the meiotics or larger doses of analogous alkaloids (morphin, pilocarpin) are required to produce the characteristic reactions.

Subjective symptoms are associated rather with minus states of muscular activation such as insufficiency of convergence, or of accommodation, resulting in asthenopia.

The Pituitary Eye.—Pituitary dominance is indicated by a roomy and massive orbit with unusually thick bony margins resulting in large, widely spaced eyeballs (Negro, Polynesian). This unusual interpupillary distance together with an apparent lack of convergence of the visual axes gives to the facies a characteristic detached expression which has something of the childlike, the naïve in it. This dreamy gaze has been noted by travelers in the racial types mentioned, and may be confirmed by clinical observation in dyscrinisms connected with hyperpituitarism.

An indirect result of the orbital spacing is the comparatively unusual development of the accessory nasal or more properly orbital cavities and the external nose with its unusually wide glabella, broad passages and wide open nostrils. This type of eye, peculiarly enough, is found in two races which are literally marked by high pigmentation.

The eye is generally enophthalmic, recessed as in Mongolians and Amerinds, or but slightly prominent when both globe and orbit are roomy,

as in Negro types. The pupil tends to be small, sluggish, and somewhat spastic with little tendency to dilatation under sympathetic emotional stimuli. The eye motions are slow and infrequent. There is a good deal of ocular pigment. The resulting expression is that of indifference, phlegma, impassivity, with connotations of patience.

This type of eye has been described as the hypothyroidic eye (Jacobson) and is most exquisitely seen, raised to the pathological degree, in myxedema. Within physiological limits it is dull, seemingly small, apparently sunken, and lack-lustre. It may be summarily described as the antithesis of the eye of exophthalmic goiter.

Adrenal or gonadal dominance may, similarly, have its implications in ocular morphology and topography, and sexual differences be found, eventually, to depend on such variance in control. Undoubtedly the endocrin dominance has a marked influence on the rate of development of the globe, and in this connection we should bear in mind that from the biologic standpoint the axially myopic eye is a further developed organ than the short hyperopic globe. While there is not enough systematized evidence for setting up ocular types to correspond with the various endocrin categories, there does seem to be a logical basis for arranging eyes in two main divisions according as they show more or less dependence on the vagus or the sympathetic system in form, function, and clinical reaction in its wider sense.

Ocular Vagotonia.—The clinical expression of this condition is that of paralysis of the cervical sympathetic, that is, meiosis, narrowed lid fissure, ptosis, enophthalmos, and anhydrosis. The tonia is easily heightened to a spasmophilia affecting not only the extrinsic ocular and lid muscles but those of pupillary action and accommodation, and quite possibly the muscular fibers of the retinal arteries as well. This is manifested, clinically, as tonic or clonic blepharospasm, either independent or as part of various facial tics, and as relapsing retinal angiospasm (intermittent claudication of the retina). The combination of symptoms massed under the name of eye-strain are found by choice in this class, and range from headache with or without vertigo and nausea, to various reflex manifestations, themselves largely spasmophiliac. Among these we may mention, in the gastro-intestinal tract, hyperacidity, hiccough, pylorospasm, spastic constipation, and spasm of the sphincter and with a tendency to the formation of fissures and hemorrhoids. The varieties of eye-strain reflexes are endless, its manifestations, protean, appearing in the respiratory tract as nervous, dry or useless, cough, as pseudo-asthma and as laryngeal spasm with aphonia; in the domain of neurology, in the form of various tics or habit spasms, from torticollis to clownism. Even the psychical sphere may contribute its quota of symptoms in the form of emotional spasms which are preponderantly akin to dislike, jealousy, suspicion, anxiety, or morbid worry.

Vagotonic Headache and Migraine. The complaint association of more or less marked pain about the eyes and brow, over the vertex, or in the occipital region, radiating at times to the neck and shoulders, and included in the term of headache, is so usual in ametropia and eye-strain that it deserves more than passing mention and some study from the endocrinological standpoint.

As a purely ophthalmological consideration we must bear in mind that eye-strain with the largely spastic local and reflex symptoms scheduled above is predominantly a legacy of hyperopia with or without astigmatism. Furthermore, it is significant that small degrees of refraction error and of muscular imbalance are often attended with what seems to be a quite disproportionate amount of suffering, and that even the most careful correction of the ametropia even to quarter-dioptries and half degrees of cylinder axis not infrequently fail to relieve. In vain, as has been said, do we pile prismatic Pelia on nasal Ossa. The patients come to us with a bushel of spectacles, all carefully fitted, and—persistent headache and eye-strain. On the other hand, we are often surprised to find decided refraction error in the course of examination of patients who say they have never had a headache in their lives. This may be explained in part by the fact that minimal errors interfere but slightly with vision and what is more important, with the effort to obtain perfect vision. In the more marked ametropias, especially the myopic forms with decided deterioration of vision, there is no incentive, if it may be so called, to strain the muscles of fixation or of accommodation. On the contrary, the choice of short range eye work by these subjects brings about an automatic adjustment between visual exertion and visual acuity which is beyond the range of the hyperop whose troubles increase as his work is brought nearer to the eyes.

These optical factors do not, however, account for all the phenomena of ocular headache, eye-strain and its reflexes, or of the vertigo and, most significant of all, of the migraine with which it is so frequently associated. This symptom has some decidedly vagotonic ear marks, including its exquisite and familial and hereditary character noted by Barker, who also calls attention to its frequency in hypertensives whose tendency to migraine is a constitutional inferiority based on a labile vasomotor nervous system.

Migraine and related types of headache seem to affect by preference individuals of a certain endocrin type and inheritance. The females of this species are relative hypothyroids, with much pigment, hair, and fat irregularly and abnormally distributed, a viraginoid or frankly masculine (adrenal-pituitary) make-up both structurally and temperamentally, and invariably show late, scanty and painful menstruation. The lack of thyroid immunizing hormone is indicated by tendency to pimples and other skin infections; the adrenal dominance, by hair on the shins and upper lip,

and the occurrence of pigmented moles; vasoconstrictor influence, by cold extremities, inability to stand Winter weather. These migrainettes are spasmophilic to excess, have a pituitary mentality, with a mind for music and rhythm, order and system, business and management, and a temperament to match, which is domineering, suspicious, inquisitive, and often jealous.

Migraine is, however, by no means limited to, or disproportionately frequent in females. If there is any predilection, it is for the student, the sedentary, the middle-aged, in short, for the scholar, who is in all three groups. It is remarkable how many scientists, comparatively, have been subjects of migraine. A number of them have described their own history and symptoms with the accuracy and minute attention to detail one would expect. Airy was one of the first.

The vagotonic connotations of migraine as a spastic phenomenon akin to retinal angio-spasm and epilepsy, refer to the analogous spasms in tetany, and to a possible dyscrinism in similar angio-spasms, of which morbid pallor and morbid blushing are the physiological prototypes, such as erythromelalgia, angina cordis, thrombo-angeitis obliterans, and possibly, symmetrical gangrene. The effects of fear, cold, fatigue, via the sympathetic system, on vascular balance, are well known (Bard). The relation of the acidotic and spasmophile factors is indicated in the vascular changes, hemorrhages, and resulting trophic disturbances, particularly of the extremities in scurvy, pellagra, and diabetes.

The spasmophilic character of migraine is accentuated by its occurrence in formes frustes, in which there is tonic or clonic spasm of the retinal arteries which might be called an intermittent claudication. These attacks have been observed during ophthalmoscopic examination. It is suggested further, to my mind, by the incidence of a migraine attack with such a vagotonic manifestation as acute indigestion with stomach cramp.

These considerations, observations accentuate the difficulty of determining in the given case whether headache and migraine are due to an actually determined refraction error or whether they are coincidental to a certain largely pituitary type. For practical purposes of therapy and, possibly, of prophylaxis both factors should be borne in mind.

To sum up, headache with migraine is one of many vagotonic disturbances in clinical ophthalmology, occurring in vagotonic (hypothyroid) individuals, of a vagotonic (hyperopic) eye form, associated with other vagotonic manifestations (spasmophilia) which we have called reflex, and often relieved less by lenses and prisms than by belladonna or other cycloplegic alkaloids which may have been instilled primarily for the purposes of ophthalmoscopic examination and accurate determination of refraction, but which incidentally, but none the less effectually, overcame the vagotonia, ocular and systemic.

Other vagotonic manifestations are an extremely low pulse and a definite increase in urinary activity with copious, pale urine.

In the female, the attacks often coincide with menstruation, and in many cases were interrupted during pregnancy, and ceased entirely with the menopause. The male climacteric has a similar good effect in generally putting an end to migraine in men.

The endocrinological implications of headache, migraine, and epilepsy are numerous and significant. On the one hand we have the association with vagotonia and its relation to spasmophilia. This again refers to acid states, defective calcium metabolism, and their dependence on defective thyroid and parathyroid secretion and their causal relation to tetany and rickets. The influence of pituitary gland disturbances in disease and with vascular changes in health incident to digestion, menstruation, pregnancy, and endocrin activation, notably thyroid, thymic, and adrenal, is so striking and important that more detailed notice of it will be taken in the chapter on hypophyseal disorders.

Cycloplegics in Eye-Strain.—It is something more than a coincidence that the alkaloids used in accurate determination and measurement of refraction errors are typically vago-paralysant, and the symptoms of eye-strain are largely vagotonic. This may in part explain certain inconsistencies and discrepancies in the data of clinical ophthalmology. Thus, the varying effect of correction of ametropia, the disproportionate severity of eye-strain in minimal errors of refraction and muscle imbalance, the excellent effects of atropinization and of correction under full cycloplegia, the adjutant effect on spasmophilic reactions, not only local and ocular but at a distance, from continuation of the belladonna treatment, finally, the marked individual reaction to refraction error, depending on what we are justified in assuming as an endocrin disposition, and manifested often enough as reflex disturbances of various functions, digestive, motor, or cerebral. In this connection I am tempted to review the biological clinics of famous ametropes if I may so call them, published by Gould, some ten or fifteen years ago, in which the life tragedies of various artists and literary men were ascribed to refraction error and its results in eye-strain and reflex neuroses. A knowledge of endocrinology throws an entirely new light on this series, and many of the symptoms which Gould considered pathognomonic of myopia or astigmatism are undoubtedly due to typical disturbances of emotion and function on a basis of disturbed internal secretions. Stated briefly, the dyspepsia, nervous instability, hyperacidity, jealousy, insomnia, anxiety and doubt states, excessive inhibition, dizziness, were not due to ametropia, but both were indications of an underlying dyscrinism.

Ocular Sympathetico-tonia.—The clinical data of this condition are not as easily interpreted as those of the opposite state of vagotonia which, as we have seen, is manifested by a variety of, mainly spasmophile, clin-

ical symptoms. The typical pathological extreme is presented by exophthalmic goiter and from this to practically normal conditions with a hyperthyroid tendency there is a logical and regular gradation. The local, ocular, effect of sympathetic irritation will, of course, depend on the amount, plus or minus, of inherent vagotonia, and on the final balance between the two vegetative influences. It follows that minor degrees of sympathetic irritation depending on hyperthyroidism will impress the observer, clinically, as a defect of vagus tone, and be expressed ophthalmologically as accommodative defect, insufficiencies of the external ocular muscles, or fatigability of the retina, or hypersensitiveness to light, or tendency to hyperemias, all of which, as we have seen, are included in the categories of asthenopia, retinal, accommodative, or conjunctival.

Emotional stimuli and sensory irritation cause, largely, sympathetico-tonic ocular reactions, such as mydriasis, dilatation of vessels in the conjunctiva and possibly in the retina, lowering of accommodation and fixation energy, and lachrymation.

When unaffected by external stimuli the eye seems to be under vagus control, as indicated by the contraction of the pupil in sleep and in narcosis.

Hyperthyroidism.—For clinical purposes, the ophthalmic signs and symptoms of this condition, as far as we know at present, are summed up in the term sympathetico-tonia. Under approximately normal conditions in health we note characteristic reactions accompanying emotional excitement, notably rage and sexual erethism. Such are, dilatation of the pupil, flushing of conjunctiva and lids, enlarged lid-fissure and prominence of the globe, with infrequent winking.

The individual reaction, vagotonic or sympathetico-tonic, to strong emotion, particularly anger, may depend on whether there is a basic, pituitary-adrenal or thyroid dominance, indicated by stature and complexion as well as by other features such as hair distribution. The very dark types would react with pallor, bradycardia, muscular contractions, narrowing of the pupil and lids; the blonde types, with flushing, exophthalmos, rapid heart action, and a dilated pupil. The English novelist Meredith says somewhere that there are only two kinds of human beings, those who turn white and those who turn red when enraged.

With subsidence of the emotion, all these reactions pass away. Where the emotion or similar sympathetico-irritant factors are repeated or become habitual or chronic, we may say that the ocular reactions border on the pathological. From this point there are easy and regular stages to the milder types and formes frustes, and finally to the typical cases of exophthalmic goiter.

Akin to the formes frustes of exophthalmic goiter is the ocular syndrome described by Lamb and ascribed by him to thyroid hypersecretion.

In these cases there was slight exophthalmos, with dilated pupils, insufficiency of convergence, and asthenopia with ciliary congestion and fatigue. Chorioretinal changes, usually in the macular region, were not uncommon. Many of the subjects show a lack of somatic as well as of ocular pigment, and general symptoms of an overacting thyroid.

Ocular Symptoms in Exophthalmic Goitre.—The sympathetic irritation which attends this serious affection is expressed, vividly in a number of characteristic states involving the pupil, the lids and lid-fissure, and the position of the globe in the orbit. The lid-fissure is wider than usual, owing partly to a lack of tone of the sphincter orbicularis palpebrarum and increased action of the levator palpebrae superioris, and partly, no doubt, to prominence of the eyeball itself. This may, in the initial stages, be due to sympathetic irritation of the unstriped muscle fibers in the orbit, but as will be noted later on, this factor alone fails to explain the persistence of exophthalmos after extirpation of the thyroid and even, as noted by Schirmer, after death. Hypertrophy of the orbital fat, with possible inflammatory changes resulting in the production of more or less solid tissue, is undoubtedly the main cause.

The characteristic expression of wide-eyed horror is due to this pathological stare (Gifford's sign) which is accentuated by marked infrequency of winking (Stellwag), lack of fixation convergence (Moebius) and, not infrequently by the dilated pupil.

Incoördination of the associated action of the levator with the extrinsic ocular muscles is expressed by a lagging behind of the upper lid when the eyes are made to fix an object above the horizontal and gradually move downward exposing an area of white, allowing the sclera to appear above the upper margin of the cornea (Graefe's sign).

Symptoms such as are usually found in hyperthyroidism have been noted in cases of persistent thymus. Besides the typical symptoms, various observers have reported alopecia and loss of eyebrows and lashes, disturbances of lachrymal secretion, either as epiphora or as loss of tears, and ocular bruit, synchronous with the pulse; optic nerve atrophy and neuritis. Tyson notes an increased stare, due to hypertonus of the levator, on attempted convergence.

Prominence of the globe in Basedow's disease and other hyperthyroidic states was quite generally attributed to sympathetic irritation of the unstriped muscle fibers in the orbit, in spite of the fact that the protrusion was unaffected by pressure on the globe and persisted after thyroidectomy and even after death (Schirmer). This spoke against such a neuromuscular theory and in favor of a mechanical element. This was found in fat hypertrophy of the orbit, with markedly increased vascularity, and, at times, connective tissue hypertrophy. Thomson noted a conjunctival chemosis attending exophthalmos which had an

almost solid consistency, and progressed when the other symptoms of hyperthyroidism had been brought to a standstill. Removal of fat tissue of the orbit has been found necessary in order to allow reduction of exophthalmos and protective covering of the unduly exposed cornea by tarsorrhaphy.

Hyperthyroidism. In a number of cases of hyperthyroidism Suker has described a condition of deficient complementary fixation in lateral eye rotation caused by dissociation of the sympathetic and oculomotor branches to the extrinsic eye muscles after extreme abduction. The clinical manifestation consists in insufficiency of convergence or actual divergence of the ocular axes on attempting to fix an object in the median plane at short range, after extreme associated abduction to either side for even a brief period.

Optic atrophy, choked disc, and optic neuritis have been noted in Graves' disease and after the experimental administration of thyroid extract to dogs, or its therapeutic use in myxedema and obesity in women.

Hypothyroidism. Within the physiological limits we can imagine a mild hypothyroidism which depends on a temporary overstimulation of the gland or too great a demand on the hormone reserve. Such a relative hypothyroidism might be expressed, in the sphere of immunity, by a similarly temporary and passing tendency to infection, particularly to colds; in the sphere of neurology, say, by a headache or by pain in the back; in the digestive sphere, by sudden loss of appetite or by sour stomach or cramp; manifestations largely vagotonic. In connection with these suggestions we must consider such actual observation of acute attacks of gout, of gall-stones, and of renal colic after a sudden fit of anger or other emotion, the sudden onset or recrudescence of arthritis, lumbago, or sciatica, after exposure to cold, a sleepless night, or exhaustion from overexertion. The thyroid reserve, as is well known, is depleted by various factors such as repeated infections, emotional stress, and possibly by certain drugs.

Physiologically this drain is soon made good automatically by the organism itself. It appears that passive as well as active exercise, heat, radiant energy, notably sunlight, aid in restoring the thyroid hormone reserve, and that certain drugs, notably belladonna, iodin, and the alkalines are valuable adjuvants.

Hypothyroidism of a more decided and lasting character is noted as a result of repeated functional disturbances, or organic changes in the thyroid as a result of disease, or possibly by marked overaction of antagonistic glands of internal secretion.

The most marked and pathological forms are, however, found in those conditions in which, as a result of operative removal or of grave disease, congenital or acquired, the hormone action of the thyroid was completely

cut off. The resulting clinical pictures depend, of course and mainly, on whether the hormone privation took place before or after the inception, or, again, the completion of various developmental and nutritional processes. The best known forms are the thyroid and parathyroid privations (myxedema and tetany), the congenital athyreoses (cretinism, Mongolian idiocy) in all of which about the same ophthalmic signs of hormone lack have been observed.

Thyroid extirpation has been followed by grave degenerative changes in the cornea which became porcelain white and densely opaque. Leber ascribes the disturbance of nutrition to toxic endothelial necrosis. Halsted noted severe conjunctival reaction, and various observers have called attention to neuroretinitis, papilledema, or partial blindness without ophthalmoscopic findings. Parathyroid extirpation, similarly, results in a grave disturbance of calcium metabolism, resulting in acidotic or vagotonic activation of muscle tissue (spasmophilia) which is reflected in clinical ophthalmology in the form of ciliary muscle spasm and hypersecretion of tears (Falta, Kahn).

Myxedema. Edema of the lids, with a resulting narrowing of the palpebral fissure, marginal blepharitis with sparse and brittle brow-hairs and cilia. The oculocardiac reflex of Dagnini-Aschner is generally greatly intensified, showing a marked vagotonia.

Mongolian Idiocy.—This peculiar type of congenital dyscrinism is strikingly hereditary but familial grouping cannot always be shown as far as the ocular defects are concerned. Besides the characteristic and striking Mongolian fold or epicanthus, there is a marked upward and outward slant of the lid-fissure in most of the cases, adding to the Chinese appearance (Casey Wood). Blepharitis and ectropion, as well as nystagmus have been noted, with strabismus and hyperopic refraction. Cataract of the punctate variety is the most frequent ocular affection. There are no characteristic vitreous or fundus changes.

Tetany. Cachexia-thyreopriva is associated with but one characteristic ocular disturbance, the formation of cataract. A relation to spasmophilia, as in all forms of lenticular degeneration, is obvious, as is the factor of disturbance of calcium metabolism which plays an important rôle in other functional and developmental disturbances of the eye in other hormone and vitamin privations.

Hormone Deficiencies and Ocular Affections.—*Parathyroid Privation.* —The spastic inhibition of nutrition becomes evident as interstitial keratitis and degenerative cataract which Coats brings into direct relation with convulsions, epilepsy, and zonular cataract in similar states. The lens changes in parathyroid privation are analogous to those in the teeth which, as is well known, show diminished calcification of dentine, diminution of bone salts, and hyperplasia of the enamel.

Ocular Affections of Pituitary Origin

Minor pituitary disturbances are frequently associated with headache, transitory disturbances of vision, or evanescent defects in the visual field, some of which assume the clinical form of scintillating scotoma, amaurosis partialis fugax, or transitory hemianopsia with a dazzling character and irregular zigzag outline of the scotoma, the so-called fortification scotoma (teichopsia). Vascular disturbances alone are sufficient to cause such symptoms after sexual excesses or too free-carbohydrate ingestion in fatigue, menstruation anomalies, and other conditions which disturb the balance between the adrenals and the pituitary, and this etiology explains the frequently temporary character of the visual disturbances and their frequent immediate relief by restoratives such as rest, the local application of heat to the brow or orbits, strong coffee, or on the other hand by brisk purgation, or derivation. Crowding of the pituitary body against the sellar wall by actual hypertrophy may cause repeated or continuous headache with visual field disturbances which continue until in some cases the syndrome is finally brought to an end by a breaking down of the bony wall of the sella at its least resistant point, allowing free expansion of the growth. In some cases the general manifestations were those of acromegaly, in others the adiposo-genital syndrome of Froehlich, from which Timme concludes that the X-ray picture of a small or occluded sella with erosion does not allow us to draw definite conclusions as to the clinical somatic type to be expected, as the point of least resistance of the sella, rather than the pituitary gland itself, is the determining factor. Where enlargement takes place laterally, there is a tendency to encroach on the cavernous sinus and cause pressure on the vessels (internal carotid, central artery of the retina), and nerves, notably those supplying the extrinsic ocular muscles and the ophthalmic division of the fifth, causing attacks of ophthalmoplegic migraine characterized by visual disturbances, pain, and single or combined ocular palsies. Changes in the posterior clinoid processes and marked reduction in size of the sella were noted in cretins by Timme who advises the administration of pituitary gland extract in addition to thyroid so generally given with effect only up to a certain point. The incidence of obstinate headache in status thymicolymphaticus is also attributed largely to the pituitary (Timme).

Ocular Disturbances in Hypophyseal Disease.—(*Bitemporal limitation, later hemianopsia.*)—The visual symptoms, consisting in typical defects in the fields for color and form, with the underlying optic atrophy or retrobulbar neuritis are to be attributed to the effects of local pressure, and in lesser degree to coincident increase in intracranial tension. The coincidence in some cases of an endocrin factor is indicated by the

antecedent amblyopias of DeSchweinitz, which become manifest as transient or fluctuating central mist without definite deterioration of visual acuity, and subjective sensations of metamorphopsia, as well as by the good effects of glandular therapy upon the amblyopia, in the form of thyroid, either alone, with anterior lobe or whole gland extract, or in conjunction with mercurial inunctions (DeSchweinitz). Pigmentation of the skin of the lids suggests a complicating disturbance of adrenal function.

Physiological swelling of the hypophysis in normal pregnancy and consecutive shrinking after delivery are cited by Schirmer in explanation of passing bitemporal hemianopsias during the last period of pregnancy in multiparae and of amblyopia which showed none of the retinal changes (albuminuric, uremic) to which such visual disturbances are generally, and correctly, ascribed. Similar visual disturbances coming on with the menopause, or after operative removal of the ovaries, are in logical accord with the hypothesis of a relative hyperpituitarism as one, at least, of the causative factors.

Oppenheim described, as tabes pituitaria, a form of locomotor ataxia with degenerative changes in the lumbar cord which he brought into relation with dyspituitarism. Schirmer advances the suggestion that some forms of optic nerve atrophy may, similarly, be due to dyscrinism in pituitary disease rather than to mechanical causes or increased intracranial pressure.

Amaurotic Family Idiocy. The visual disturbances, marked ocular changes, myasthenia, and general debility, with periodic convulsions, and fatal termination form a well known clinical picture. The endocrin implications of this and allied cerebroretinal degenerations of infancy may be summed up as indicating an indirect or inherited congenital vulnerability, on a basis of syphilis or more probably avitaminosis in the mother, of the adrenal elements promoting normal nutrition and metabolism in the central nervous system. This familial toxemia may be associated with lesions in the thymus, adrenals, and thyroid.

Hereditary Optic Nerve Atrophy.—(*Leber's Disease.*)—This condition has been placed by some observers in the group of congenital endocrin disturbances. The familial grouping, the incidence at puberty, or at the climacteric, the association with various neuropathies, are advanced as suggestive significant facts. Definite changes in the sella, indicating pituitary enlargement, were noted in a series of cases by Zentmayer and others. Optic atrophy in steeple skull or oxycephalus is probably due to synostosis of cranial sutures, notably the sagittal sutures, and consequent mechanical interference with the nutrition of the optic nerve rather than to a direct effect of dyscrinoid heredity factors, although the latter may have some significance in the causation of the original developmental anomaly of the skull itself.

Adiposis dolorosa is at times associated with amblyopia, and cases are

on record in which, after amblyopia had been present for some time, vision was raised to 7/15 by the administration of pituitary extract (hypophysin). Acromegaly and gigantism are hyperpituitary in origin and the characteristic facies as well as coincident disturbances of vision are manifestly dependent on changes in the region of the sella turcica and the consequent alteration of growth relations in the orbit.

Cases of dyspituitarism with failing vision, down to loss of light perception, homonymous hemianopsia and marked general symptoms, extreme pallor and weakness, drowsiness and severe headache have been restored to normal by hypodermic injections of pituitrin, 1 c.c. daily, after oral administration had failed to affect the symptoms and subtemporal decompression produced only temporary relief (Elsberg, Krug) and pituitary tumor has been successfully treated by administration of thyroid and pituitary extract combined with mercurial inunctions in definitely nonluetic patients (DeSchweinitz, How). Eason reports the case of a patient who was practically blind, but recovered normal vision and nearly a full field in one eye after thyroid feeding. The improvement had persisted for nine years; the patient had to take small doses of thyroid from time to time to prevent recurrence of blindness and headache. Elsberg says that operative procedures such as sellar decompression, partial excision by the transfrontal route, etc., while not dangerous in experienced hands, are only palliative in the majority of instances, and suggests that in field defects of hypophyseal origin, if associated with evidences of secretory deficiency or cyst formation, a thorough course of hypodermic treatment with glandular extracts should precede any operative interference.

In a similar case with increased drowsiness and headache and feebleness in a female with hyperpituitary markings, notably of the hair and teeth and orbits, Timme observed that corpus luteum, administered tentatively because the constitutional symptoms and visual disturbances increased with the onset of menstruation and during its term, regularly caused an immediate aggravation of the condition. Thyroid, gr. ½, alternating with whole gland pituitary, gr. 1, daily, and adrenalin in 5-7 drop doses, later whole gland suprarenal, gr. 2½, twice daily, by mouth, completely relieved the systemic symptoms and the visual fields returned to normal, while vision remained but slightly affected, 20/40, as before.

Vascular Disturbances.—Ocular hemorrhages, notably retinal, are prevalent at puberty. They were formerly classed as vicarious menstruation. Now, generally attributed to tuberculosis, and indeed reacting, usually, to diagnostic injections of tuberculin, with focal, local, and general disturbances. Often with low blood pressure and indications of dysthyroidism. Lack of calcium and disturbance of coagulation indicated by beneficial effect on pulmonary hemorrhages of calcium chlorid 10 per cent, 5–10 c.c., 2–5 X, q. d. Hemorrhage activation in thyroid

disturbances simulating tuberculosis. In ocular hemorrhages with blood diatheses and deficiency diseases, as purpura, scurvy, look for a dyscrinism. Tachycardia, like that in exophthalmic goiter, is seen in scurvy (Hess) with oliguria suggesting the action of atropin and relative lack of pituitrin.

Vascular disturbances in lids and conjunctiva are common in hyperthyroidism as well as in angioneurotic states due to acidosis. Wilmer notes the cure of recurrent vitreous hemorrhages in a young man by removal of pyorrhea foci and clearing out intestines.

Barker is impressed with the importance of constitutional inferiorities of the vascular, the nervous, and the endocrin systems in the pathogenesis of chronic arterial hypertension, and of chronic renal disease. Patients with obesity, diabetes mellitus and gout tend to develop an arteriosclerotic process and many of them also have high blood-pressure. The retinal indications of arteriosclerosis may be observed in a very beautiful picture on ophthalmoscopic examination. The earliest stages consist in a narrowing of the reflex or light streak on the smaller arteries and a slight change in color producing the copper-wire appearance noted by many observers. An increased rigidity of the vessel wall is also shown by arteries where they pass over veins in a compression of the underlying vessel with a resulting damming of current and local dilatation of the vein on the proximal side and a narrowing for a short distance on the distal side of the crossing. Irregularities in caliber, particularly of the smaller vessels, are frequent. Tortuosity of arterial twigs is a somewhat later change, as are actual degenerative changes in the vessel wall indicated by grayish patches on or alongside the arteries, showing lime deposits in intima or media. Peri-arteritis is also observed, with a double outlining of the vessel. In all the later stages hemorrhages may be seen, generally from superficial arteries and involving the nerve fiber layer as indicated ophthalmoscopically by their flame or horsetail shape. After repeated hemorrhages, degenerative changes are found in fatty yellowish spots with blood pigment traces or in bright white points, sometimes confluent to patches, indicating calcification. The significance of renal disease and of diabetes in the causation of retinal hemorrhages and neuroretinal inflammation is well known, and the fundus changes need not be described *in extenso* here. These affections and some other factor, such as arteriosclerosis or arthritism, have been noted in the much less frequent but interesting condition of retinitis circinata in which the wreath-shaped arrangement of the confluent degenerative patches in a double bow from optic papilla to macula gives a name to the fundus condition and marked interest to the ophthalmoscopic picture. The origin of these degenerative spots, later areas, from small almost capillary hemorrhages has been noted by the writer and various other observers, one of the first of whom was the late Edward Fridenberg.

Subconjunctival hemorrhage or spontaneous ecchymosis is by some to be accepted as an indication of a tendency to ocular hemorrhage, generally of unhealthy blood-vessels, and especially as a danger sign pointing to possible retinal hemorrhage. In advanced age this may be of significance, but in infancy and youth such hemorrhages may be caused with normal blood-vessels by sudden and excessive increase in pressure with vomiting, or with spasmodic coughing (pertussis).

Lid hemorrhages, particularly the petechial variety as seen in malignant enodocarditis and in the systemic hemorrhagic diseases such as purpura hemorrhagica and pernicious anemia—these, as well as massive orbital hemorrhages, have been seen in infantile scurvy (Barlow's disease).

The similarity of these conditions to the clinical syndromes due to vitamin deficiency is striking. Like scurvy, of which the deficiency factor is known, there are others like pellagra, and probably purpura rheumatica, in which the vitamin or hormone defect has yet to be found, although there is little doubt of its agency.

The therapeutic indications of ocular hemorrhages as far as metabolism and the endocrins are concerned coincides completely with the desiderata of treatment of the underlying conditions or of actual organ disease (Bright's, diabetes, cardiac disease) in other parts of the body.

The prognosis, it should be borne in mind, must consider the special delicacy and vulnerability of the retina, in which respect it is like the brain, and retinal, like cerebral hemorrhages, in their damaging effect on the functional activity of the perceptive elements of which both tissues are so largely made up.

Ocular hemorrhage, or more particularly retinal, is common in the secondary anemias and, as one would expect, in such systemic conditions as pernicious anemia, leukemia, as well as in certain grave intoxications particularly with the hemocytolytic poison such as rattlesnake poison.

Most of the observations on intra-ocular hemorrhage date from a period in which little attention was paid to general metabolism or its disorders, and none at all to the internal secretions. A re-survey in the light of our present knowledge of endocrinology would be of great practical value.

Uveitis.—The etiology of inflammations of the iris, ciliary body and choroid is concerned chiefly with syphilis in its various stages, tuberculosis, gout, rheumatism, gonorrhea, putrefying intestinal accumulations and focal infections. In the light of endocrinological study these factors have an added and a different significance from that of a specific microorganism, toxin, or protein which happens to localize in the uveal tract and cause infection or inflammation. In acquired lues there is probably an actual invasion of the ocular tissues by the spirochete. In gonorrheal iritis such invasion is highly improbable and the agency of a gonorrheal toxin has been generally accepted in its place. The mode of action of pus accumulations in the teeth, accessory nasal cavities, tonsils, gall-bladder,

appendix, or prostate is likewise dependent more probably on a transported toxin than on any actual metastasis of micro-organisms or of pus cells from the foci of infection. The special relation of these etiological factors to endocrinology lies in their deleterious action on the glands of internal secretion and particularly on the immunizing function of the thyroid. From this point of view special importance attaches to the chronic, inveterate forms of sepsis or toxemia producing relapsing or low-grade sluggish uveitis which is notoriously bad prognostically and difficult to treat with any degree of satisfaction either to patient or physician. The virus of syphilis and of tuberculosis, meaning the germ-free but toxic protein, seems to be on a par in this respect with the poison absorbed by the organism from pyorrhea alveolaris, apical abscess, and chronically diseased tonsils.

The therapeutic implications are interesting and significant, showing without exception that all our remedial agents tend, perhaps by various paths, to a single end, that of stimulating the sympathetic system, depressing the irritated vagus, and restoring the depleted thyroid. This applies emphatically to catharsis, irrigation of the lower intestinal tract with subsequent alkalinization. It applies, as well, to restriction of carbohydrates and lowered diet, to massage and exercise, to sweats and hot baths.

The traditional local treatment of iritis by hot applications, instillations of atropin and dionin, and by the abstraction of blood from the immediate neighborhood of the globe by leeching, gives logical support to this view. Such local treatment is usually fairly successful in acute attacks of iritis or uveitis in other forms, but frequently fails in the chronic relapsing cases. This indicates clearly, I think, that there is in those very cases an organic hormone deficiency to be made good, probably by appropriate organotherapy, as the mere stimulation of the system is not enough. The source is dried up; a new supply is needed.

The influence of the thyroid gland has been noted by Dunn, who says that owing to its extreme vascularity, the ciliary body is very responsive to blood changes which often make their appearance some time after the thyroid has become exhausted in its efforts to overcome a toxemia of intestinal or other origin, and find in the ocular tissues a diminished resistance to bacillary infection or protein sensitization.

Dunn reports a number of remarkable cures from the administration of thyroid extract in iridocyclitis and other deep seated eye affections. The dose of the extract employed by him for children beyond five years of age and for adults is three grains twice daily, and from this dosage he has never seen any ill effects.

Bordley (Baltimore) has had a fairly large number of similarly good results in the treatment of malignant uveitis with thyroid which he thinks valuable mainly in restoring the defensive biological processes of

the organism. Bordley gave 2½ grains of iodothyrin from one to three times a day.

Enlarged and diseased tonsils are significant, not only as portals of infection but, from the endocrinological standpoint, as indications of a lymphoid hypertrophy which is generally associated with adenoids and indicates an acidotic, vagotonic tendency. In such tendencies, as in the exudative diathesis there is a marked relative lack of thyroid immunizing power and a resulting disposition to colds and susceptibility to infections. Both features play a rôle in the uveal affections. Exposure to cold and wet is an important etiological factor in many uveitis cases which would formerly have been classified as idiopathic in the absence of a known specific disease cause. Here there is a close analogy with rheumatism, which is itself so frequent a basic constitutional factor in certain forms of iritis associated less with plastic exudation than with serous effusion, much pain, and not infrequently, increased intra-ocular tension. Arthritism is probably more injurious by way of disturbed metabolism and, secondary, hormone-immunity destruction than by any other action. The good effects of heat, massage, and the change of symptoms for the worse with increase of pain in cold, wet weather are as striking in the ocular involvement as in the joints and muscles.

The clinical symptoms of uveitis may in a way be said to indicate vagotonia in the contracted pupil, pain, and tendency to plus tension. Repeated paracentesis of the anterior chamber has been observed to act favorably by reducing tension and also possibly by removing a chemically altered (acidotic?) secretion and allowing the entrance into the eye of uncontaminated fluids. This stimulation of intra-ocular metabolism undoubtedly plays a part in other therapeutic procedures such as leeching.

Skin Affections of the Eye.—The skin of the lids is naturally affected by many dermatological diseases. The conjunctiva of lids and globe is, in a way, modified skin, and the same may be said of the epithelium and superficial layers of the cornea. Accordingly, we find typical disturbances of these tissues in constitutional diseases characterized by skin manifestations, particularly in the acute exanthemata.

The lymph follicles of the lids show a condition of hyperplasia with little inflammatory reaction, quite like adenoids, in children with tonsils and pharyngeal lymph nodes. Parinaud's conjunctivitis, Mikulicz's disease, and mumps of lachrymal gland and palpebral follicles are analogous.

Eosinophilia. Blepharitis, red lids, chronic hyperemia of the lid margin, and various skin affections such as dry, seborrheic eczema, and relapsing styes. Causes, refraction error, pus foci (teeth, tonsils, intestine, sinuses, etc.), with relative hypothyroidism or deficient thyroid immunity. Aided by calcium (sulphids), intestinal lavage, and yeast, a single dose of calomel.

Falling out of lashes and eyebrows. Herpetic rash of the lid skin

and conjunctiva has been observed after application of bluestone for Parinaud's conjunctivitis.

Styes. High blood sugar and probably lowered sugar tolerance in furunculosis (Gettler and St. George). Furuncles, gangrene in diabetes. Good effect heat, calcium sulphid, yeast, from endocrin standpoint.

Organotherapy. Secretin, thyroid, to activate metabolism rather than anti-diabetic diet.

Blepharitis and red lids. Persistent and relapsing hyperemia of the lid margin with occasional secondary infection of the hair-follicles of the lashes producing repeated crops of styes has been observed in conjunction with other manifestations of eye-strain in obstinate refraction error, in connection with focal infections (teeth, tonsils, sinuses) and toxemia, as well as in plethoric, constipated individuals with a gouty tendency. The indication of a thyroid lesion in the predisposition, or at least in the etiology, is clear, and this is borne out by the fact that many accompanying symptoms pointed to a pathologically dominant vagotonia, while the most successful therapy with calcium sulphid, bakers' yeast, intestinal lavage and calomel referred to a restoration, stimulation, or substitution of thyroid activity.

The skin, as a mirror of the system, is a faithful index of various metabolic and endocrin disturbances which appear not only in the integument of the eye, the lids, but in other ectodermal ocular structures as well, notably the cornea and lens.

Senility affects not only the lid-skin (pigment, atrophy) but the cornea (gerontoxon) and lens (cataract). Familial occurrence of one or more of these changes at an early age as an expression of dyscrinoid pre-senility is not uncommonly observed in a familial grouping and hereditary incidence. Xeroderma pigmentosum, which is essentially an atrophy with pigmentation and epithelial hyperplasia, has been included in the expressions of pre-senility on a basis of syphilitic (hereditary) dyscrinism. It is often accompanied by other changes in the superficial tissues of the eye, notably the conjunctiva, such as atrophy, or essential shrinking, leading to entropion, and with telangiectases of the lids and conjunctiva. Other ocular dermatopathies indicating a metabolic or dyscrinoid influence are edema of the lids, chemosis of the conjunctiva, seen frequently after the ingestion of certain foods (strawberries, crab-meat, buckwheat) or medicines (quinin, antipyrin). Urticaria and Quincke's edema often appear on the lids and conjunctiva, at times associated with iritis, mydriasis and paralysis of accommodation as an expression of a marked metabolic constitutional disturbance, markedly hereditary, which is indicated, further, by frequent association with edema of other parts of the body, notably the larynx and pharynx, cheeks and lips, and penis. In this connection we may note also the coincidence of exudative erythema of the lids and conjunctiva with arthritic symptoms, especially in children.

Phlyctenular affections of the conjunctiva and cornea were always associated by clinical observers with disorders of metabolism in specially predisposed subjects. The frequent association in scrofulous children with eczema, either local (ocular) or general and interpreted less as part of a skin affection than as a parallel manifestation of a diathesis, variously characterized as arthritic, lymphatic, or exudative, is well known.

Phlyctenular Keratitis and Conjunctivitis.—Clinically a manifestation of lymphatism. Helped, empirically, by cleaning out intestine, relieving toxemia, eliminating tea, coffee, pickles, sweets, etc., from dietary, administering alteratives, rhubarb and iron, iodides and, moreover, insisting on fresh air and hygienic mode of living. Diagnosis, scrofula, seen with glands of the neck, pasty skin, eczema, exudative diathesis, chronic intestinal intoxication. The tuberculosis theory of the etiology of phlyctenular affections brings in all of these factors as links in the causal chain. The good effect of calomel locally and per os, of the yellow oxid of mercury as an eye-salve, is largely due to stimulation of processes of repair.

Keratitis ex Acne Rosacea. This is a form which is clinically very similar to phlyctenular keratitis, but appears in adults as an expression of a severe and long standing disturbance of metabolism. It begins with infiltrations at the limbus which become ulcerated and afterwards acquire a serpiginous character, with tendency to invade the center of the cornea. The arrangement of inflammatoy blood-vessels in leashes running to the ulcers, later faint leucomas, is typical of this fascicular keratitis. In some cases hyperemia of the iris or mild iritis has been noted, and occasionally there is a development of inflammatory nodules or papules in the sclera which generally undergo absorption and disappear without any sequelae. Simple rosacea is never attended by ocular complications. Gastrohepatic and intestinal, as well as menstrual, disturbances are common etiological factors in the anamnesis. The combination of trophic disturbance and general toxemia with an irritating infectious agent is probable (Uribe-Troncoso). An angioneurotic element in the etiology and clinical course connects these cases again with the exudative diathesis, Quincke's edema, and other dyscrinoid, probably hypothyroid, states.

Lymphatic States.—The conjunctiva shows follicular hypertrophy often diagnosed as trachoma, but which never runs the severe course of that disease, and is benign in its outcome. Often seen in children with adenoids, "buck teeth," and constant colds.

(*Good effects of C. L. O. Fe. Iodin Adrenalin.*)

Other forms of conjunctival, ocular, lymphoid hyperplasia seen in Parinaud's conjunctivitis, and in involvement of lachrymal gland and conjunctival follicles in Mikulicz's disease and epidemic dacryo-adenitis

(mumps of the lachrymal gland), with status lymphaticus, and enlarged thymus. Possible connection with protein sensitization, acidosis, exudative diathesis, hyperchlorhydria, pylorospasm, and acid stomach.

Vernal Conjunctivitis, or Spring Catarrh (Saemisch) is similarly, a lymphoid affection of the conjunctiva of the lids and of the circumcorneal area of the ocular conjunctiva. The lymphoid hypertrophy of the palpebral conjunctiva often shows progressive tissue changes with toughening to a horny consistency. The papillary hypertrophy around the cornea is on the contrary always gelatinous, never more consistent. The condition is most obstinate, annoying, and shows a marked tendency to relapse at about the same time each year, that is, just after the final disappearance of cold winter weather. Constitutional and local treatment of every kind has been tried with practically no effect. Local applications of astringents are worse than useless as even very weak solutions cause marked reaction and aggravate the condition, which tends gradually to disappear with the advent of hot summer days and cool fall days. Of late, *x*-ray and radium treatment and instillations of fibrolysin have been reported to act well, as do adrenalin solutions used locally. Marked pigmentation was noted in many but by no means all of the patients. This and the similarity in some ways to trachoma and other follicular lymphoid conditions of the lids associated with acidotic states and adenoids, and the beneficial effect of adrenalin suggest the therapeutic administration of thyroid gland on the supposition of a relative hypothyroidism due to overacting pituitary and adrenals.

Vitamins and the Visual Organ

The importance of vitamin disturbances in disorders of nutrition has an important bearing on the metabolism and function as well as the structures of the eye. The physiology of the vitamin supply has not been worked out, and it is a question whether these substances normally supply a chemical which is itself essential to life or whether they act indirectly to stimulate the endocrin glands in their nutritional functions, and serve as activators of hormones. The latter agency is indicated by the apparent inability of the organism to store vitamins and produce a reserve or to synthetize any one of these important substances from diets which contain all the basic organic and inorganic constituents of fat, carbohydrate, or protein food. The analogy and even partial identity of hormone and vitamin action is indicated by functional and organic ocular disturbances which are found, on the one hand, in typical dyscrinisms of an hereditary character, and again in definite avitaminoses. The interrelation of metabolism and endocrin supply is indicated in disturbances of fat digestion, in acidotic states, and in faulty calcium metabolism, all of which are generally accompanied by characteristic disturbances of the eye. Calcium

lack is suggested in the dystrophic lamellar cataract of rickets, and in the trophic disturbances of the cornea and sclera in this disease which are analogous to the changes in the bones throughout the body. Special local conditions, notably intra-ocular secretion and tension, are responsible for reactions which are peculiar to the eye, such as the distention of its pathologically non-resistant and excessively elastic coverings which result in megalocornea, bouphthalmos, and probably infantile glaucoma, so called. The markedly hereditary character of these structural anomalies is another link in the chain which connects the eye with both hormone and vitamin supply.

Visual Disturbances.—As has already been noted, visual disturbances of a uniform and characteristic nature are seen with certain congenital abiotrophies, and again in apparently normal eyes, under the influence of starvation, exhaustion, or the experimental withdrawal of one or the other vitamin. Hemeralopia is the common symptom in retinitis pigmentosa, in avitaminosis, and in certain chronic disturbances of hepatic metabolism. The relation of pigment to vision is indicated again by the histological changes in the ocular tissues and by the fact that coloring matter seems to be a characteristic of certain necessary food-elements. Thus Steenbock concludes that the fat-soluble vitamin is related to certain yellow pigments found in butter, sweet potatoes, carrots, maize, and spinach. Spoiled maize plays a rôle in pellagra, and in this disease and in scurvy, degenerative processes with a marked pigmentary relation (nails) are found.

There are certain endocrin-metabolic implications in therapy, as well, such as the beneficial effect of cod liver oil in starvation hemeralopia, in the cataracts of acidotic hypothyroid states, the interstitial keratitis of rickets and lymphatism, and in tetany. As the administration of calcium itself seems to be of little value, the question arises whether this element or the iodin in cod liver oil, a synthetically produced calcium, or a combination of these elements, is the essential, and, finally, whether the reaction is purely metabolic or not rather connected with chemical activation of the thyroid.

Xerophthalmia and Keratomalacia.—This affection has been observed in rats, mice, young rabbits, and children as a result of a deficiency in the diet of so-called fat-soluble vitamin (A). As histological examinations showed no corneal changes in consonance with the name given, the condition is to be referred to simply as ophthalmia. Wason found hyalinization of the corneal epithelium with signs of bacterial invasion and of productive inflammation and vascularization in Bowman's membrane and in the substantia propria. The corneal degeneration progresses to a generally perforative ulceration which may lead to the protrusion or extrusion of the lens. Simple inanition and infection have been excluded as possible causes of this condition although, of course, there is almost always

secondary infection which may account for some at least of the serious sequelae such as perforation of the cornea and panophthalmitis. The factor of traumatism must also be considered.

The lessened resistance produced by lack of fat soluble vitamin first becomes apparent in many cases of rats by a characteristic infection of the external eye which has been provisionally classified as xerophthalmia.

Stephenson and Clark found invasion of the cornea by leucocytes to be the first change. Later, edema and swelling of the cornea and an interstitial keratitis were noted but they failed to demonstrate any histological change in the cornea preceding bacterial invasion. Similar changes with early cornification of the epithelium were reported by Freise, Goldschmidt, and Frank. The nature of the pre-inflammatory lesion which produces the degeneration, loss of nutrition and marked susceptibility to infection has not, so far, been discovered by histological examinations and its nature can only be hypothesized (Wason). The well known specificity of chloroform for the liver cells, of mercury for the epithelium lining the convoluted tubules of the kidney, and of tetanus toxin for the central nervous system may serve as analogues. The importance of secondary bacterial invasion cannot be ignored (Wason).

The eye symptoms promptly cleared up on administration of the fat-soluble vitamin in the form of butter-fat, less quickly with alfalfa oil or spinach oil.

Young animals are particularly susceptible to deficiency of fat-soluble vitamin (Drummond and Coward), and in substantial harmony with this is the further fact, noted by Osborne and Mendel, that ophthalmia is a rare occurrence in more mature animals.

Xerosis, essential shrinking, of the conjunctiva, has been noted in man in connection with hemeralopia, or alone, in starvation states, and in undernourished native children as a Brazilian ophthalmia sui generis (Gama Lobo). The presence of a specific microörganism (B. xeroseos) and the similarity to pemphigus indicate an infectious factor. Whether this is primary or not has not been determined, but it seems probable that the pathogenesis is quite analogous to that of avitamin corneal xerosis.

It is worth noting that conjunctival instillations of milk and other animal fats have been followed by marked and rapid improvement in this obstinate, progressive, and serious condition.

Keratoconus is a hypothyroid manifestation, associated with lowered intra-ocular tension and tonus, and lowered nutrition of the cornea. Abderhalden dialysis tests applied in three cases of this condition by v. Hippel, showed disturbed metabolism involving the thymus, suprarenals, and thyroid.

Endocrin Therapy in Ophthalmology

The largely empiric character of organotherapy in eye disease has as a result that we have many suggestions and implications, with comparatively scanty data of a definite and well authenticated sort. A philosophic, scientific attempt to rationalize our methods of treatment, from this point of view, must bear in mind some of the basic factors of immunity, metabolism, and physiology recounted under the various headings of this survey. Constitutional treatment, either of general or of ocular disease, must recognize a probable endocrin factor not only in diet and drugs, but in heat and cold, rest and exercise, sleep, sun and shade, nay, even in mothers' milk.[1]

As far as specific organ products are concerned, general principles will indicate the importance of correcting disorders of metabolism or of endocrin balance. The choice of the gland or glands, and of activating adjuvants from the dietary or the pharmacopœia, will be determined largely by physiological chemistry and by a clinical diagnosis which considers not only the ocular symptoms but the systemic reaction to special tests of endocrin function. This is the only basis for a rational therapy.

Clinical observations on organotherapy in particular ocular affections have been concerned with uveitis, glaucoma, and admittedly dyscrinoid eye-states as noted in the preceding chapters. The implications are largely constitutional and causal, rather than local and symptomatic. The latter phase suggests a brief study of the traditional and accepted procedures of ophthalmic medication from the endocrinological point of view. This indicates that many of our valuable ocular remedies act, at least in part, by virtue of their vagotonic or sympathetico-tonic action.

Ophthalmic Pharmacodynamics.—The two main classes of ophthalmiatric alkaloids, the meiotics and the mydriatics, are characterized as much by their selective action on the two branches of the vegetative nervous system, as by their well-known and striking pupillomotor influence and the resultant or accompanying action on ocular hyperemia and inflammation, on intra-ocular tension, and so on.

Heat and cold, local abstraction of blood by leeching or cupping, darkroom cures, sweating and catharsis, as well as systemic alkalinization have been used with good effects in a wide range of ocular diseases on a largely empiric basis of clinical observation. Iodids and mercury are, admittedly,

[1] Endocrinology gives us a new and broader view of what was accepted unquestioningly and fatalistically as Nature's way of healing, a way which, as often as not, killed instead of curing. We may safely assume that all Nature's telluric influences act on and by the complicated system of the glands of internal secretion. How else can we attempt to explain the systemic effects of such influences as wind, weather, altitude and climate, seasonal incidence and geographic distribution of disease, and so many others?

of great value in ocular conditions, notably choroidal affections, in which a specific luetic basis could be excluded.

A marked individual reaction to meiotics and mydriatics is seen in health and disease, and the factors of age, sex, epochs, and general condition are well worth further study. The details of the action of these alkaloids on the physiological processes and pathological conditions of the eye have been studied and reported so fully by Lewin and Guillery, and others, that a reference by the writer to those sources of information must suffice.

The use of adrenalin as a hemostatic and as an adjuvant to astringents to reduce hyperemia in conjunctivitis and similar superficial ocular inflammations and to aid the action of cocain as a vasoconstrictor and anesthetic before ophthalmic operations is a well established procedure.

Action on pupil. Ordinarily, adrenalin does not affect the pupil, as the vagotone of the sphincter under physiological conditions is sufficient to overcome any weak dilator pupillae action. Similarly, sympathetic irritation under emotional stimulus will cause mydriasis only in as far as there is loss of vagotone. Thus, in glaucoma or in a tendency to pathological plus tension, even a weak solution of adrenalin instilled while the pupil is small may produce a rapid dilatation and rise of tension and halo vision. The provocative instillation of cocain in weak solutions acts similarly, and this is the more striking as, at the age at which glaucoma is most common, there is, in normal eyes, a decided (vagotonic) resistance to mydriatics, expressed in a tendency to small pupils, a certain rigidity of the iris, and an intolerance to meiotics, such as eserin, which are very apt to produce symptoms of iritis. In Zentmayer's résumé, there is a statement to the effect that suprarenal extract produces mydriasis when the sympathetic is paralyzed, after extirpation of the thyroid, in exophthalmic goiter, and following the administration of thyroid extract. I have been unable to reconcile these contradictory statements.

Endocrin Therapy.—*Epinephrin.*—There is no reason for believing that adrenalin has any effect on the intra-ocular tension of normal eyes. In glaucoma, it first lowers, then raises, and finally again lowers, tension. This may be secondary to the mydriatic action described above, as extreme dilatation of the pupil in middle or old age is apt to find topographical conditions of intra-ocular filtration which predispose to an acute attack of glaucoma. Loss of the normal vagotone, which as we have seen, tends to keep down intra-ocular tension, is strikingly indicated by this reaction, as well.

Seasonal Incidence.—The prevalence of a disease at a certain time of the year has been generally attributed to prolonged cold or heat, bad hygienic conditions, such as overcrowding, defective ventilation, lack of food, gastro-intestinal toxemia from these factors as well as from constipation, and lack of exercise. The practical validity of this assumption has been

shown in some cases by the beneficial effect of hygienic and dietetic regulation, yet a link is missing in the pathogenetic or etiological chain. The *modus operandi* is not clear, and is not made any more so by reference to intestinal auto-intoxication, anemia, or indicancuria.

There is reason to believe that all the agencies mentioned bring about a relative deficiency of endocrin secretions (hormones), and that the symptoms of seasonal disease, not a few of them ocular affections, are manifestations of deficiency which can be favorably influenced by appropriate endocrin therapy. It is quite probable that there is, apart from this, a seasonal ebb and flow in endocrins depending partly on climatic and temperature factors and on the other hand on the needs of the organism. (It has been shown for instance that there is a wide variation in thyroxin and adrenalin content in the glands of winter-killed and of summer-killed animals, respectively.) This, like all periodicity, is largely under the control of the pituitary; thus, hibernation in animals is dominated by this endocrin gland. The prevalence of certain ocular affections in warm weather such as that of Saemisch's spring catarrh cannot be explained so easily by the purely hygienic factors mentioned above. The basic process, that of lymphoid hypertrophy, associated the disease in our minds with others like adenoid hypertrophy, tonsillar and Mikulicz's disease, and Parinaud's conjunctivitis. In these ocular conditions, there is an eosinophilia which is probably of endocrin origin and is seen, as we have noted elsewhere, in a large number of hormone deficiency states associated with acidotic vagotonia (asthma, migraine).

SECTION XIV

Gigantism, Dwarfism and Infantilism

Gigantism ..... *Peter Bassoe*

Classification—Gigantism with Infantilism—Characteristics of Infantilism—Hypophyseal Infantilism—The Influence of the Gonads on Growth—Eunuchoidism—Distribution of Growth Disturbance—Examples of Combined Gigantism and Infantilism—Congenital Syphilis and Gigantism—Gigantism with Acromegaly—Examples of Cases of Gigantism with Acromegaly—Gigantism and Leontiasis Ossea—Gigantism with Infantilism and Acromegaly—Gigantism in Childhood—Heredity in Gigantism—Association of Gigantism with Other Abnormalities—Metabolism in Gigantism—Localized Giant Growth—Hemihypertrophy.

Gigantism

PETER BASSOE

CHICAGO

"Gigantism is an anomaly of skeletal growth characterized by an excessive height of the individual as compared with the average of his race, and exhibiting a morphologic and functional disharmony characteristic of this morbid state" (Launois and Roy).

Henry Meige (*b*) was the first (1902) to insist that a person merely very tall but otherwise normal should not be called a case of gigantism. That such a restricted use of the term is not a violation of the English language is shown by the definition of gigantism given in Webster's "New International Dictionary" of 1914: "Development to abnormal size accompanied by various stigmata such as disproportionately large extremities or marked facial asymmetry, and usually by constitutional weaknesses. Development to unusual size but with normal physique is not giantism." [1] To obviate confusion with "normal" excessive growth the terms "macrosomia" (Malacarne, Taruffi) and "somatomegaly" (Dana, Meige) have been proposed but they have not been generally used and to-day in medicine the term gigantism is accepted as standing for a morbid condition and not a normal variation. As a matter of fact, all persons of giant size who have been studied in recent years by modern methods, including the X-ray and close scrutiny of the endocrin glands, have been found to be abnormal. The "normal giant," the physical superman with strength and energy in proportion to his size, belongs to legend rather than in the realm of critically observed phenomena. Launois and Roy point out that the pathologic nature of gigantism was understood by the encyclopedists of the eighteenth century as Diderot and Alembert's *Dictionnaire encyclopedique* contains this statement: "When giants attain the the height of seven or eight feet they are most frequently badly formed, ill, and incapable of exercising the commonest functions."

References to giants abound in the myths and legends of all races.[2]

[1] *Giantism* is apparently given preference to gigantism as a better English word, but the latter is generally used in medical literature.

[2] Most of these are assembled in the book of Garnier, "Les Nains et les Géants," Paris, 1884. A very complete historical review is also found in the monograph of Launois and Roy. The latter work, on which we draw very heavily in this article, gives lengthy abstracts of practically the entire literature, lay and medical, dealing directly or indirectly with gigantism up to the year 1904.

For practical purposes we may distinguish the following epochs in the evolution of the study of gigantism.

1. The period of myths and legends.

2. The historic period up to the time of Darwin and Virchow, or the middle of last century. Very little precise information was recorded.

3. The anatomic and anthropologic period from the middle of the last century until the description of acromegaly by Pierre Marie in 1886. Many giants were well described and subjected to postmortem examinations. Minute measurements of living patients and of skeletons were recorded but the cases were regarded as anatomic curiosities and no true clinical conceptions were elaborated.

4. A very active period of investigation, revision and contention which followed the prompt recognition of acromegalic features in many living giants and skeletons of giants (approximately 1890-1905). There was a lively exchange of views between those who favored the idea of the essential identity of acromegaly and gigantism (at first chiefly Italian investigators), and those—principal among them Marie himself —who considered the two diseases distinct entities which only occasionally coincided.

5. The present period, inaugurated by the fundamental investigations of Brissaud, Meige, Woods Hutchinson, and Launois and Roy, which were carried on for some years preceding the appearance of the first exhaustive monograph on the subject by the last named authors in 1904. The facts so ably compiled in this work, and subsequent observations, among which perhaps the most interesting and convincing are those of Harvey Cushing (*c*), have clearly established gigantism as a disorder related to disturbed endocrin function, the hypophysis playing the most important, but by no means the entire rôle.

Classification.—It is noteworthy that almost all giants described in the last twenty years, the period during which consideration has been given to endocrin disorders, fall in one of the following groups:

1. Gigantism with infantilism.
2. Gigantism with acromegaly.
3. Gigantism with infantilism and acromegaly.

In the earlier reports attention had been paid chiefly to the skeletal changes, which usually had been minutely described, while the hypophysis frequently was not mentioned at all, as in the case of Buhl's otherwise excellent description of the famous giant Thomas Hasler. In 1897 Maximilian Sternberg gave an excellent résumé of the status of the giant problem. He recognized the existence of "normal" giants, among whom he placed Virchow's case, Winkelmeyer, 227.8 cm. tall. His classification of "pathological" giants was as follows:

1. Acromegalic giants—about 40 per cent of the total.
2. Cases with multiple tumor-like exostoses (leontiasis ossea and hyperostoses).
3. Cases with facial hemihypertrophy.
4. Cases with multiple curvature of the bones of rhachitic character.
5. Gigantism in hereditary syphilis.
6. Gigantism in connection with testicular tumors in children.

This was the best classification possible on the basis of the data available at that time but it is obviously superficial and merely an index of certain features which had been emphasized by the respective authors.

Gigantism with Infantilism

Characteristics of Infantilism.—Infantilism is discussed in another chapter, but for purposes of orientation the salient features may be reviewed here. Meige defines infantilism as "a developmental anomaly characterized by the persistence in a person past the age of puberty of morphologic features belonging to childhood." [3] The most important of these features as a determining factor in giant growth is delayed union of the epiphyseal cartilages beyond the normal age. The genital organs, external and internal, are more or less rudimentary and functionally useless. The menses do not appear. The secondary sexual characteristics, such as beard, pubic and axillary hair, adult voice, etc., are not attained. It must, however, be emphasized that stunting of growth need not be a feature. Infantilism is a condition entirely apart from dwarfism. Either may exist without the other though they may be combined. Typical infantilism is seen in people of normal size as well as in giants and dwarfs.

Hypophyseal Infantilism.—That infantilism may primarily depend upon hypophyseal deficiency in the absence of thyroid defect is stoutly maintained by A. Souques and S. Chauvet. The genital hypoplasia is considered secondary. Several cases have been examined post mortem and the hypophyseal lesion confirmed. Cushing prophesies that ultimately all cases of hypophyseal infantilism will come to be grouped together whether they exhibit adiposity or not.

The Influence of the Gonads on Growth.—In the search for understanding of gigantism and dwarfism in connection with infantilism it is incumbent on us to consider the possible effect upon growth of the deficiency of the sexual glands *per se*. The effects of castration are particularly suggestive. Like capons, eunuchs are prone to be of large

[3] The term infantilism was first used in the present sense by Lasègue.

size, with long and straight extremities. Very instructive and interesting is the study of the "Skoptzi," members of a cult originating in Russia, many of whom emigrated to Roumania. They practiced castration on a large scale and have been described by a number of observers.

Thus, Tandler and Grosz described two types—one tall and thin, the other fat and bloated, with broad pelvis and large fat deposits in the buttocks, breasts, and in the regions of the trochanters and pubis. The extremities are very long, while the head is small, with flattened occiput, prominent superciliary ridges and enlarged sella turcica. The pelvis is wide; genu valgum is common. The epiphyseal lines remain open. The hair on the head is thick but a growth of beard is lacking except that in old persons there may be one, of the type seen in old women. The larynx is small without ossification of the cartilage. The thyroid is small but the thymus may persist. Attempts have been made to attribute the growth increase following castration directly to the gonad defect. The favorable effect of castration in promoting osteogenesis in osteomalacia has been recalled, as have observations of decreased urinary excretion of phosphoric acid in castrated individuals. Sacchi's case of a child with testicular tumor who reached a height of 143 cm. (4 ft. 6½ in.) at nine years has also been pointed to in this connection. However, the matter is more complicated. Cushing points out that castration or destructive testicular disease in the preadolescent causes hypertrophy of the hypophysis to the effect of which the abnormal growth is to be ascribed.

Eunuchoidism.—Eunuchoidism was first described by Griffith and more precisely defined by Tandler and Grosz (*b*) (*c*) as a developmental disorder from defect of the testicular interstitial glands, with faulty development of the secondary sexual characteristics, abnormal persistence of epiphyseal lines, and fat deposits like those of eunuchs. It has recently been lucidly discussed by H. Fischer. The main physical characteristics, according to him, are: Long extremities, small trunk, elongated skull, broad malar bones, deep root of nose, marked lateral development of the lower jaw, steep occiput, broad pelvis, genu valgum, abnormal persistence of epiphyseal lines and of cranial sutures. Furthermore, underdeveloped genital organs, fatty deposits on the chest, lower abdomen, pubis, pelvic crest and outside of thighs. There is little hair on the face and body while that on the head is thick and does not tend to fall out with age. Fischer lays great stress on the disproportionate length of the extremities, while cases with great adiposity usually belong in the hypophyseal group, and those with marked skin changes and carious teeth in the group of thyroid deficiency.

Distribution of Growth Disturbance.—G. Papillault lays down the following rules for the build of the infantile giant:

1. The trunk is of nearly normal size and the excessive length is in the extremities.

2. The lower extremities are relatively longer than the upper.

3. The proximal segments of the extremities (femur, humerus) are relatively less increased in length than the distal segments.

4. The hand and the foot are a little less increased in length than the fingers and toes.

Examples of Combined Gigantism and Infantilism

1. The giant Charles, 30 years old, height 204 cm. (7 ft. 8 in.), described by Launois and Roy, had weighed 21 lbs. at birth (?), was very tall at 12 years and measured 186 cm. at 21, 194 cm. at 24. His upper and lower extremities were unduly long, and there was marked genu valgum. The genitalia were poorly developed, the testicles rudimentary, the prostate not felt on rectal examination. Sexual desire and power were absent. There was neither beard nor axillary hair, and very scant pubic hair. The hands and feet were disproportionately large: not so the lower jaw. Röntgenologic examination showed that at the age of 30 years his epiphyseal lines remained open. His intelligence was fairly good but he was somewhat emotional and ill tempered.

2. Bramwell describes a man, 50 years old, 6 feet 3½ inches tall, who began to grow rapidly at 20 years. The fingers were long and tapering. The penis and testicles were very small; there was no beard, axillary or pubic hair, and the voice was childish. He was deficient mentally. The cause of death was heart disease. Post mortem the hypophysis was found not to be enlarged, and the thyroid was small.

3. Jödiche's case is typical of this class and remarkable on account of the family history. The father was 235 cm. tall and died at 55 years of carcinoma of the lung. The paternal grandfather was said to have been a giant, and the father's younger brother was "very large." There were three older brothers of the patient, measuring respectively 180, 185 and 184 cm. and an older sister 168 cm. The patient was 22 years old, measured 205 cm. and weighed 79 kilos. He had always been large but grew very rapidly between the ages of ten and fourteen years. He was of a very low intelligence and energy, sluggish in everything except eating in which he indulged to excess. His voice was that of a child. The penis was of a size normal in a boy of five years, the testicles and prostate very small. There had been no signs of genital function. The thyroid was not enlarged. There was no growth of hair on the face, pubes, or in the axillæ. Further evidence of infantilism was revealed by the open epiphyseal lines in the hands. The thyroid was palpable. The bones were delicate, the arms and legs were very long, and hands

and feet proportionate. The sella was not enlarged and there were no abnormal eye findings. The only suggestions of a tendency to acromegaly were a broad nose, broad tongue, and rather prominent lower jaw and chin. The author relates the gigantism in this case wholly to the deficiency of the genital glands.

4. Fahærus describes a man, 24 years old, 192.5 cm. tall, beardless, of infantile appearance, who had attained his full height prior to the removal of both testicles, when he was 20 years old, on account of tuberculosis. The abnormal growth was attributed to loss of the internal secretion of the testicles on account of the tuberculosis. The same author briefly describes a similar case in a man of 38 years, 197 cm. tall in spite of a marked kyphosis, whose left testicle was not discoverable.

Fig. 1. Ella Ewing, the Missouri giantess. (Photograph secured at a County Fair in Iowa.)

5. Georges Thibierge and Pierre Gastinel report the case of a man 188 cm. tall (6 ft. 4½ in.), 52 years of age. It was stated that when 12 years old he was a head taller than other boys of his age. The authors describe him as a type of infantile gigantism with features of feminism: he had no growth of beard, a childish voice, underdeveloped testicles and absence of sexual desire; the shape of his hips, the prominent abdomen and breasts gave him a feminine appearance. The thyroid was very small.

6. One of the tallest and best studied giants on record is properly placed in this class, namely, John Turner, described in Cushing's monograph. He measured 251.5 cm. (8 ft. 3 in.), and weighed 275 lbs. His sexual function had never been developed, and he had extremely scanty beard and pubic hair. The most striking sign of infantilism, however, was the persistence, at the age of 36 years, of the lower epiphyseal line of the radius. The hands were huge, but the fingers tapering and not spade-like as in acromegaly. In the skull the upper facial bones, i.e. upper jaw and malar bones, were disproportionately large, rather than the lower jaw, and the tongue was not unduly large. The necropsy

findings were remarkable: a brain weighing 1884 gms; a large, cystic hypophysis; large spleen, kidneys, and liver; small thyroid, adrenals, testes, and pancreas.

This appears to be the heaviest brain on record with one exception, that of Turgenief which weighed 2012 gms. (Gilford).

Launois and Roy also place in this class the well known but imperfectly studied cases of giant Winkelmeyer, described by Virchow, and the Missouri giantess, Ella Ewing, reported by Woods Hutchinson (*a*). Virchow considered Winkelmeyer a "normal" giant but Hutchinson points out that his height at the iliac crests is 64 per cent of the total instead of the normal 55 per cent, and the same disproportion is found in Ella Ewing.[4]

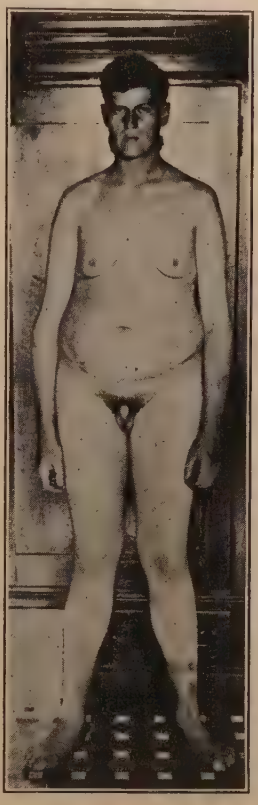


Fig. 2. Gigantism; Infantilism and Feminism. (Personal observation.)

7. The following unpublished case of infantile gigantism is largely interesting on account of the family history. The patient was seen in 1903 when seventeen years old. He stated that his father was between 56 and 60 years old, measured 7 feet 8¾ inches, weighed 380 lbs., and had enormous hands. This giant father had been married three times. By his first wife he had no children, by the second nine, all boys, of whom the patient is the youngest. The second son measured 6 feet 4 inches, the fourth 7 feet 1 inch, the sixth 6 feet 8 inches. The others were of usual size. The third wife, herself a giantess of 7 feet 6 inches and weighing 420 lbs., presented him with four daughters of usual stature. Two paternal uncles measured, respectively, 6 feet 10 inches and 6 feet 3 inches. (I had no means to verify any of these data.)

The subject was born in Würzburg, Germany, Dec., 1885. He did not go to school but learned to read German and can write somewhat. He cannot read English but speaks it fluently without foreign accent. He has never been seriously sick, but has headache occasionally and pain through the ears. He has worked as canvass man with a circus. He thinks he measured 5 feet 10 inches at the age of 12 years, and that he has grown one inch in the past year.

[4] The photograph of Ella Ewing reproduced on page 812 was secured by me at a county fair in Iowa where she exhibited herself in 1900. She claimed to measure 8 feet 4 inches and to weigh 256 lbs. and to be 26 years old. Her features look somewhat coarser than in the probably somewhat earlier pictures in Hutchinson's article which suggest that an "acromegalizing" process possibly was commencing. In a letter of July, 1920, Dr. Hutchinson informs me that she was living and well three years ago.

His appetite is excessive. He was given double rations when with the circus. He smokes cigarettes and chews tobacco; he does not use alcohol.

Every month for two or three days he has pain in the sides and hips, the face flushes, but no blood appears anywhere. He has no sexual feeling, never masturbated, and once was put to bed with a woman without any desire being aroused. No erection ever occurred.

His measurements follow:

Height 192 cm. = 6 feet 3½ inches.

Height of iliac crests	126	cm. (60.67% of his total height)
Head measurements:		
Fronto-occipital diameter	18	cm.
Glabella-inion (arc)	36.6	"
Biparietal diameter	14.7	"
Bimastoid diameter	12.7	"
Binauricular diameter (just above meatus)	12.5	"
Binauricular arc (same points)	35.5	"
Distance between zygomas (by pelvimeter)	13	"
Circumference of head (horizontal)	54	"
Greatest width of nose	3.5	"
Other measurements:		
Between iliac crests (pelvimeter)	31	"
" trochanters	33.5	"
Symphysis pubis to base of sacrum	20.5	"
Circumference of neck over larynx	34	"
" of chest	93	"
" of abdomen at umbilicus	100	"
Length of penis	5	"
Circumference of penis	6	"
Diameter of glans penis	18	mm.
Length of scrotum	5	cm.
Circumference of scrotum	12	"

	Right	*Left*
Length of arm (acromion to tip of middle finger)	82 cm.	79 cm.
Acromion to external condyle of humerus	37.5 "	35.5 "
Length of hands (tip of radius to tip of middle finger)	20.2 "	20 "
Length of thumb	6.4 "	6.2 "
Circumference of arm	28 "	26 "
" of forearm	26 "	25 "

	Right	*Left*
Circumference of wrist	16.5 cm.	16 cm.
" of thigh	59 "	58 "
" of knee over patella	41 "	41 "
" of calf	40.5 "	40.5 "
Length of foot	27.3 "	27.2 "
Width of foot at base of toes	12 "	11.8 "
Height of knees	55 cm.	
Width of shoulders across back	39 "	

On *physical examination* he appears like an overgrown child, simple mannered, very frank and good-natured, and will do anything he is told to do. His head is relatively small and face comparatively thin. The forehead is low. There is abundant hair on the head, but none on the face or other parts of the body than the axillæ and pubes. No cranial nerve disturbance is found. The nose, tongue, mouth, lips and lower jaw are not at all enlarged. The tonsils are not enlarged. The palate is not deformed. The thyroid gland is not enlarged; it can be felt. The lower part of the neck is thick, the upper rather thin. There is a prominence over the upper part of the sternum at the level of the third rib. The trunk is decidedly feminine in appearance: the breasts are pendulous, symmetrical, with nipples 6 mm. in diameter, surrounded by pigmented areolas, 25 mm. in diameter. No secretion can be expressed. There is a large amount of subcutaneous fat. The hips are broad. The pubic hair is 3 cm. long, its upper border being horizontal, 3 cm. above the root of the penis. The abdomen is prominent and pendulous like that of a woman who has borne children. The penis and scrotum are small (see measurements). Two very small testicles can be felt. The heart is of normal size on percussion; the apex impulse is very feeble. There is no dullness in the region of the thymus. The patellar reflexes are sluggish. Sensation is normal. The voice is high-pitched. The grip is weak. The veins about the left ankle are prominent. There are pigmented superficial scars over the left leg, anteriorly. He shows marked pes planus.

Congenital Syphilis and Gigantism

In the literature certain cases of gigantism, especially those of Sirena, Nobl, and Fuchs are attributed to congenital syphilis, and E. Fournier also includes that of Buhl (to be described later). It is probable that in some of these cases the syphilis has affected the genital organs and produced a state of eunuchoidism to which the growth disturbance is due. Thus, Werther describes and pictures a boy 16 years old, with extraor-

dinary length of the lower extremities, whose genitalia, however, were of the size normal in a boy of six years. Wieting describes a case of eunuchoid or infantile gigantism in a congenitally syphilitic boy of 18 years, 225 cm. tall, with kyphosis and genu valgum, but proportionate extremities.

Gigantism with Acromegaly

Only a few years after Marie's fundamental work on acromegaly, attention was called by many observers to the relationship between this disease and gigantism. In 1889 Virchow (*b*) recognized a certain similarity between those two conditions but not any kinship. In 1892 Massalongo stated that acromegaly is nothing but delayed, abnormal gigantism. The identity of the two disorders was further advocated by Brissaud and Meige (*a*) (1895) and Woods Hutchinson (*b*) (1898). The latter summarized his conclusions as follows: "1. The greater part of the overgrowth is found at or near the tips of the segment-crescents, as in acromegaly, differing from the latter mainly in that it is not exclusively confined to the tip of the segment or last division of the limb. 2. The facial part of the skull is enlarged out of all proportion to the cranial, particularly in the region of the lower jaw. 3. The condition, whether it be regarded as normal or morbid, is one that distinctly tends to shortness of life, and would appear to have an average duration of scarcely more than twenty years. 4. The mental and physical vigor of the giant is distinctly below par, and his death usually comes either from a steady, progressive increase of this weakness, or from some trifling accident, or usually mild, intercurrent disease. 5. Sexual powers appear in the great majority of cases to be far below normal. 6. There is a decided preponderance of males among the victims of this condition. In all of these statements there is a decided parallelism manifested between gigantism and acromegaly. Last of all, and from the point of view of this essay, of greatest interest is the fact that the one morbid condition which is peculiar to both of these disturbances of nutrition, the enlargement of the pituitary body, is found to be present in a large majority of cases of both." After stating that the material as yet is meager, he adds that we are "justified at least in the tentative conclusion, until some evidence to the contrary can be adduced, that acromegaly and gigantism are simply different expressions of one and the same morbid condition; in other words, that acromegaly is a general overgrowth tendency which does not, for some reason, begin to express itself until after adult stature has been reached, and which consequently expends itself upon those points in the body at which growth last ceased—the extremities of the segment-crescents and the distal extremities of the appendages. Second, that gigantism in a large majority of cases is this same condition manifesting itself in

childhood or before complete stature has been reached, and the growth in consequence is more symmetrical and less strictly confined to the last segment of the arches and appendages. In most cases, however, the tendency appears to be for these last segments to grow in an unsymmetrical and excessive manner." Finally in 1902 H. Meige stated:

1. Acromegaly never precedes gigantism.
2. Acromegaly sets in during the course of about one-half of the cases of gigantism.
3. When acromegaly is associated with gigantism the latter always appears first.

Meige added that when the disease commences in youth we get gigantism, when in adult life, we get acromegaly, and when it commences in youth and continues during adult life we get a combination of the two. This formula is in the main correct but certain reservations must be made. In exceptional instances typical acromegaly, without undue growth in height, begins in early youth while the epiphyseal lines are open. Likewise, certain giants who live beyond the growing period fail to be "acromegalized." Cushing's careful case studies clearly bring out the reason for the presence or absence of this transformation from simple to acromegalic gigantism. It occurs only when hyperfunction of the hypophysis continues after the cessation of growth. Such hyperfunction is likely to be present for a certain period only and to be intermittent. Later, hypofunction is prone to ensue but the acromegalic signs once produced obviously remain permanently.

Examples of Cases of Gigantism with Acromegaly.—In the course of the revision of all recorded cases of gigantism which followed Marie's description of acromegaly in 1886 it was shown, particularly by Brissaud and Meige, Woods Hutchinson, and Launois and Roy, that many, if not most, of the earlier giants exhibited signs of acromegaly. This is true of both of the famous "Irish giants," Cornelius McGrath (8 feet 6 inches) and Charles Byrne (8 feet 2 inches), described by D. W. Cunningham, both of whom had disproportionately large hands and feet, prominent lower jaw and enlarged sella turcica.

Among the early cases studied in America is that of a Bolivian Indian, Santos Mamai, 30 years old at death, reported by Dana. He measured 6 feet 7 inches in height, weighed 300 lbs., and had typical signs of acromegaly: large jaw, hands and feet, enlarged thorax, kyphosis, and greatly enlarged sella with hypophysis tumor. There was also a general enlargement of the viscera (splanchnomegaly). Woods Hutchinson described a somewhat similar giant, 18 years old, from Minnesota, decidedly acromegalic, as well as diabetic, and with hypophysis tumor demonstrated at necropsy. The left eye was blind owing to complete

destruction of the left optic nerve by the tumor. The frontal sinuses were huge. The thyroid and genital organs were small. Another case was the "Kentucky Giant," whose skeleton, described by Hinsdale, is preserved in Philadelphia. Nothing is known of the clinical history. Many acromegalic giants exhibit such an exaggerated kyphosis that their actual height becomes greatly reduced. This is particularly true of the giant Peter Rhyner, described in great detail in 1884 by Fritsche and Klebs, and of the Chinese giant of Matignon. The latter giant had also rudimentary and functionless genitalia so he perhaps more properly belongs in our third class. Giant Mazas, described by Brissaud and Meige, measured 212 cm. at the age of 21 and at 25 reached 220 cm.; at 37 he rapidly developed a kyphosis which reduced his height to 186 cm. at 47 years of age, but also increased his circumference at the level of the gibbus to the same figure—186 cm. He was so bent that the nipples were at the level of the anterior superior iliac spines. The tongue and the lower jaw were enlarged.

Fig. 3. Chinese Acromegalic Giant. Matignon. (After Launois and Roy.)

The giant Hugo (Fig. 4), described by Launois and Roy in their book, was seen by the writer at a circus in Chicago. The only measurement secured on this occasion was the width of his palm which was 14.5 cm. He claimed to measure 7 feet 6 inches and appeared to do so. His face, large extremities and genu valgum suggested acromegaly. Apparently, only casual observations of this man are on record. Meige also considered him an acromegalic giant.

A well-studied case is that of "Tambourmajor K," 34 years old, 212 cm. tall, first described by Achard and Loeper. His father measured 195 cm., a paternal uncle 210 cm., a sister 180 cm. "K" had measured 176 cm. at 18 years and reached his full height at 21. Broadening of the hands and face was said to have commenced at 18 years but the acromegalic features were not pronounced until a year or two before death, when he developed glycosuria. The patient died two years after

the publication of Achard and Loeper's paper, and the necropsy findings are related by Launois and Roy. There was a large hypophysis tumor. A true splanchnomegaly existed: the heart weighed 510 grams, the liver 4650 grams, the spleen 370 grams, the pancreas 250 grams, the thyroid 250 grams, and the kidneys together 715 grams.

Zondek gives a clinical description of a somewhat similar case in a Russian, Fedor Machnow, 23 years old, whose maternal grandfather was over 2 meters tall. The patient's abnormal growth began at 5 years, and he reached a height of 236 cm. His feet were 36.3 cm. long, and the width of the shoulders, 53.5 cm. During the entire period of active growth he slept a great deal. His intelligence was good. The nose, occipital protuberances and frontal sinuses were large; the sella is not mentioned. Machnow is also described by Lissauer and v. Luschan (1903), who give his height as 238 cm.

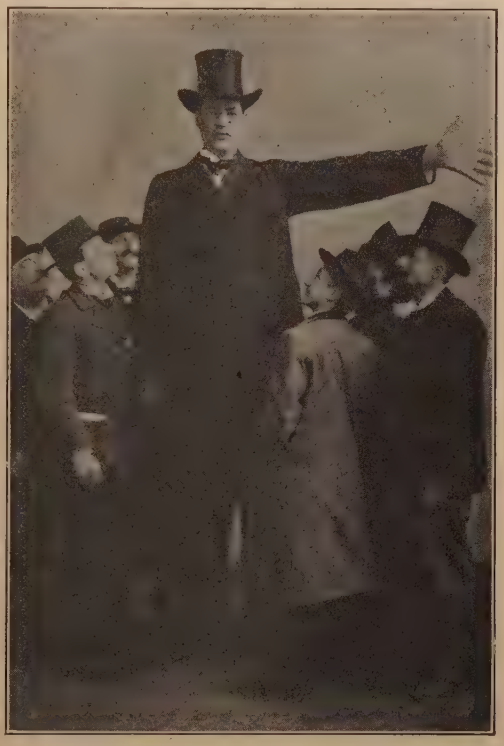


Fig. 4. The Giant Hugo. (Photograph secured at a circus in Chicago.)

Cushing relates an exceedingly instructive case in which it is clearly shown how active hyperpituitarism in childhood and early youth produced general gigantism, how a second access of glandular overactivity produced further increase in height and acromegalic features and, finally, the development of adiposity and high sugar tolerance, indicating hypophyseal insufficiency. The patient was a man 35 years old. He was a healthy 10-pound baby at birth, and developed normally until 13 years old, when he began to grow rapidly. At 19 he measured 6 ft. 4 in., and weighed 200 pounds. He was intelligent and of unusual physical strength: he could lift a 900-lb. rail to a truck. At 23 years he had a severe illness with marked polyuria, followed by persistent furunculosis. A photograph at 25 shows no sign of acromegaly. At 27 he again began to grow in height. At 28 there was severe frontal headache. At 30 vision began to fail. At 32 his features showed change, becoming coarse, and he was losing his strength, was drowsy and tired easily. The sexual power was lost.

At 35 he measured 6 ft. 6 in. and weighed 269 lbs. The blood pressure was low—75 to 100 mm. The X-ray showed greatly enlarged sella, 3.5 cm. long and 2.8 cm. deep. There was bilateral primary optic atrophy, with blindness of the left eye and superior hemianopsia in the right eye with two remaining patches of the lower field. A bilateral exophthalmos was ascribed more to change in the shape of the orbits than to venous stasis. The intelligence remained good but he was very drowsy. The circumference of the head was 64 cm. The lips, tongue and nose were very large and the lower jaw prominent, with spacing of the lower teeth. The hands were large, röntgenogram of the fingers showing characteristic tufts, exoxtoses and widened phalangeal shafts. The feet and toes were extremely large. The skin was smooth and velvety, with considerable boggy edema. There was practically no beard and only scant pubic hair of feminine distribution. The carbohydrate tolerance was estimated at over 300 gm. of glucose. Polyuria was no longer present. The thyroid was very small and the testes were soft and atrophied.

Fig. 5. Giant, Machnow, with Professor Luschan. (In the picture may be seen skeletons of a Patagonian and Bushman.)

Sellar decompression was performed in December, 1910: a piece of tumor removed showed masses of chromophobe cells separated by greatly dilated sinusoidal spaces. There was some improvement after the operation, the fields became larger and vision better and he was less nervous and drowsy than before.

Ettore Levi and Guiseppi Franchini relate a case of acromegalic gigantism in a man 66 years old, 199 cm. (6 ft. 6½ in.) tall, probably the victim of hereditary syphilis, with positive Wassermann reaction, Argyll-Robertson pupils, slight optic atrophy and loss of knee and ankle reflexes; in other words he had also tabes. His father probably has suffered from tabes. The patient began to grow rapidly at the age of 8 or 10 years. He was of a low grade of intelligence and while his sexual organs were of normal appearance he never developed sexual desire or power. He was obese but quite well proportioned as regards develop-

ment of trunk and extremities. The cranial portion of his skull was small in proportion to the face but his hands and feet though large were proportional to the body. The tongue was long and thick but not too broad. The lips were thick. The muscles were hypotonic, poorly developed and weak. There were two interesting congenital anomalies in the left eye—persistence of the pupillary membrane of Wagendorff and ectropium uvæ.

Fig. 6. Giant, Palozzi. (After Levi and Franchini, Icong. de la Salpetrière.)

The authors point out that this case demonstrated the truth of the statement made long ago by Launois and Roy: all giants who are not acromegalic are prone to become so. In his youth this man probably had been an infantile giant. The acromegalic features consisted principally in the thickening of the soft parts. The size of the sella turcica could not be determined as no successful radiogram was obtained.

This case, occurring in a victim of congenital syphilis, is allied to those reported by Fuchs (man 26 years old, height 188 cm. with many stigmata of syphilis, entirely beardless) and that of Sirena (a necropsied Egyptian giant of 240 cm. who died of nephritis at the age of 20 years. His weight at death was 218 kg. The head was deformed, with marked bony changes ascribed to syphilis. The head weighed 8300 grams. Splanchnomegaly was extreme; the heart weighing 890 grams, spleen 875 grams, kidneys 870 grams, and liver 4070 grams).[5]

Gigantism and Leontiasis Ossea

On the borderland of acromegalic gigantism we have a few remarkable cases of giants with hyperostoses of cranial and facial bones, the deformities of the latter giving to the face a "leonine" appearance, hence the

[5] The disturbances of growth, including general and localized gigantism as well as dwarfism, dependent on inherited syphilis, are exhaustively discussed in E. Fournier's Paris thesis of 1898.

name. Two cases deserve especial mention, those reported by Buhl and by Bassoe (*a*).[6]

Buhl's case was that of a man, Thomas Hasler, who was normal up to the age of nine years, when a rapid growth commenced. This is said to have followed a kick on the cheek by a horse. Some years later huge hyperostoses of the facial and cranial bones appeared and were larger on the injured side. At twelve he measured six feet. He died at twenty-

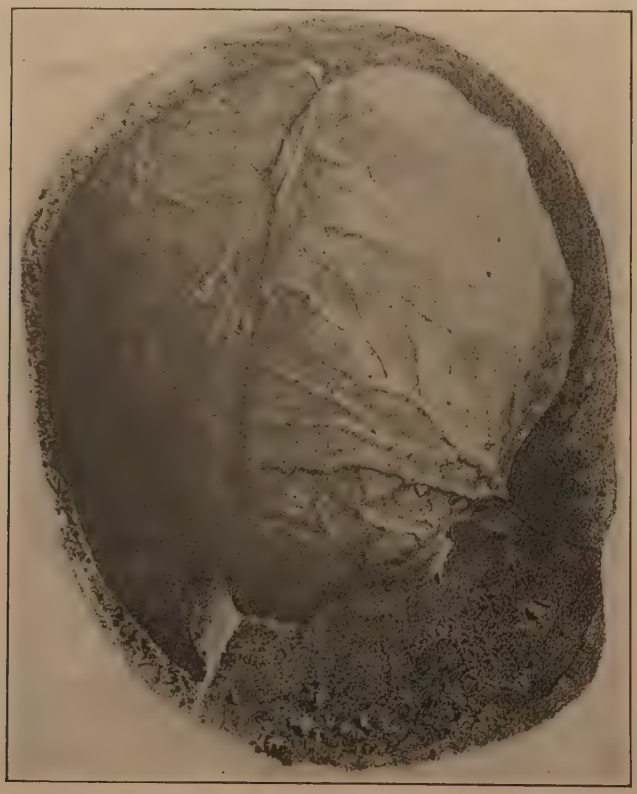


Fig. 7. Base of skull in Buhl's case. (Mitt. a. d. pathol. Institut, München.)

five. His height then was 227 cm., or 235 cm. (7 ft. 8½ in.) with the back stretched; the weight, 155 kg. There were no lesions of the viscera. All epiphyses, including those of the trochanters, were sharply outlined. The skull showed enormous exostoses. The lower jaw was very irregularly enlarged in all directions, its height at the middle of the chin being 12 cm. and thickness, 9 cm.; the left side was the thicker. The upper maxillæ were also thick. On the left side the processus frontalis, the nasal, malar, ethmoid and lachrymal bones were greatly thickened, the

[6] For no very clear reason E. Fournier in his thesis includes Buhl's case among instances of general gigantism with multiple exostosis dependent on inherited syphilis.

floor of the orbit raised, and the left wall of the nose displaced to the right. The left frontal bone measured 6 cm. (2⅜ inches) in thickness; the left temporal, 1.5 cm.; the right, 1 cm. The left side of the occipital and parietal bones also was thick. Both in the frontal and parietal bones superficial porous islands were found. The interior of the skull was diminished on the left side, the sella turcica displaced to the right. The brain weighed 1,465 grams, and was much decomposed at the time of the autopsy. The hypophysis is not mentioned. Buhl attributed the patient's death to compression of the brain.

Fig. 8. Deformity of brain from cranial hyperostosis. (Buhl's case.)

Bassoe's case was the giant Wilkins, 245 cm. tall, who died in 1902 at the age of 28 years. When 19 years old he was described by Dana. He then measured 7 feet 4 inches (223 cm.) and weighed 325 lbs. His general proportions were for the most part good, but his feet (14 in. or 35.5 cm.) and hands (10¼ in. or 26 cm. from the tip of the middle finger to the styloid process of the ulnæ) were enormous, and the left side of the face showed an osseous hypertrophy, involving the frontal, superior and inferior maxillary bones. His vision at that time was good. His muscular strength was poor. Three years later (1896) he was presented to the Medical Society of Vienna by Lamberg as a case of acromegaly, but Maximilian Sternberg and Schlesinger opposed this view, because of the absence of enlargement of the soft parts and of prominence of the lower jaw, and because the hands and feet, though huge, were in proportion to the size of the body. In 1898 Villers of Brussels designated this man as a "scaphocephalic giant" and attributed the condition to rickets in childhood. He was also examined by Virchow, and casts of his hands and feet exist in the Pathological Museum in Berlin. For several months before his death in 1902 he suffered from headache and vomiting. He became blind in the left eye, and three weeks before death in the right one also. The left side of the face was anesthetic and the left ear deaf. The left eyeball was immobile. The enlargement of the left side of the head

Fig. 9. Hyperostotic skull. (Buhl's case.)

had become more pronounced and was not entirely bony, as a soft tumor mass could be felt above the left ear. Bilateral choked disc was present. In addition to these symptoms of compression of the brain and cranial nerves the patient suffered from amebic dysentery.

The necropsy revealed enormous hyperostosis of the anterior portion of the skull, most marked on the left side (Fig. 11), causing a correspond-

Fig. 10. Giant Wilkins, and his brother. (After Bassoe, J. Nerv. & Ment. Dis.)

ing deformity of the brain (Figs. 12 and 13). The greatest thickness of the frontal bone was 8.5 cm. The anterior fossa on the left side was completely filled with bone and the middle one nearly filled. The sella turcica was wide, its floor partly eroded. A large, soft tumor mass in this region had grown into the pharynx, orbits, and ethmoid sinuses and destroyed the roof of the nose. It had grown also through the frontal and temporal bones and formed the subcutaneous tumor above the left ear and on the left side of the forehead. The tumor was shown to be a sarcoma which evidently had arisen in the hyperostotic frontal bone. The hypophysis was surrounded, but not invaded by the tumor. It was rather large, though flattened, and measured 2 cm. in length and 8 mm. in thickness.

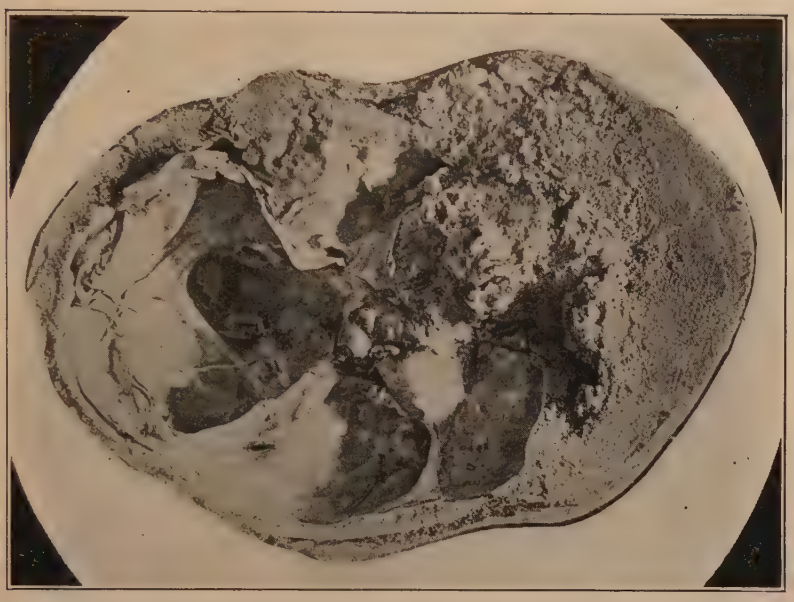


Fig. 11. Hyperostosis of skull and osteosarcoma at base of skull of Wilkins, the Giant. (After Bassoe, J. Nerv. & Ment. Dis.)

Fig. 12. Base of brain with indentations caused by hyperostosis as seen in Wilkins, the Giant. (After Bassoe, J. Nerv. & Ment. Dis.)

Its structure was described as essentially normal, but Cushing, who later examined the sections, rightly pointed out microscopic evidence of adenoma formation, indicating functional overactivity.[7] The splanchnomegaly in this case was extreme: the liver weighed 4,000 grams, the pancreas 275 grams, the adrenals 42.5 grams, the kidneys 525 grams, the heart 465 grams, and the thyroid 112 grams. The stomach, which was very voluminous, with its mucosa thrown into huge wrinkles, weighed 655 grams. The small intestine measured 20 meters in length, the large intestine 4

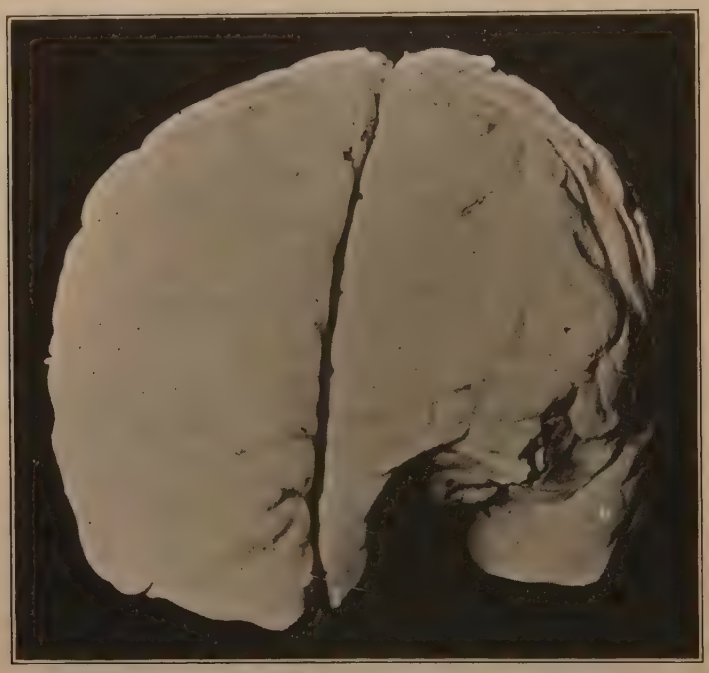


Fig. 13. Anterior view of the brain of Wilkins, the Giant. (After Bassoe, J. Nerv. & Ment. Dis.)

meters. The brain, in spite of the relatively reduced capacity of the cranial cavity, weighed 1,540 grams, and the medulla and cord measured 60 cm. in length.

Should this case be classed as acromegalic gigantism? Strictly speaking not, if we adhere to the original, purely morphological definition of acromegaly as a growth disorder characterized by enlargements of end segments. That the giant growth in this case was caused by hyperfunction of the hypophysis, however, seems certain.

A third case of this kind, also with necropsy, is that of Caselli, a man, 193 cm. tall and 30 years old at death. His genital functions were not

[7] See Cushing's monograph, "The Pituitary Body and Its Disorders," page 170, footnote.

developed, and he had no beard, axillary or pubic hair. Scoliosis was marked and the bones of the legs were badly curved. The head was large and deformed, with a prominence on the left side and a tumor on the lower jaw. The hands and feet were very large. He became blind in the left eye, and developed temporal hemianopsia in the right eye. Polyuria and glycosuria also set in. On account of the deformities his height decreased from 193 to 182 cm.

At the necropsy the skull was found to be enormously thickened, to the extent of 4 cm. in the occipital and 6 cm. in the frontal region. The large tumor of the lower jaw was found to be a spindle-celled osteosarcoma. The hypophysis was the seat of a large adenoma.

Gigantism with Infantilism and Acromegaly

Obviously, the placing of the recorded giants in the three chosen groups must be somewhat arbitrary. The distinction between the second and third groups is naturally not sharp, and in many of the cases described in Group 2 signs of infantilism were discernible. For convenience of description, however, it is useful to segregate the cases in which, in spite of the process of "acromegalization" of the infantile giant, signs of infantilism remain conspicuous.

Launois and Roy illustrate this group by the case of the giant Constantin, described by themselves and Dufrane. An uncle was said to measure 203 cm. Constantin measured 194 cm. at 14 years and then grew at the rate of 15 cm. yearly until he reached 259 cm. He developed symmetrical gangrene of the legs, both of which finally were amputated. He died at 29 years of age. The infantile features were: 1. Disproportionate length of the lower extremities. 2. Open epiphyseal lines in femur and humerus with complete separation at the upper end of the latter. 3. Undeveloped genital function and hypoplastic genitalia. The following findings proved the existence of acromegaly: (1) marked prognathism, (2) large hands and feet, (3) prominent malar bones, (4) enormous sella turcica and hypophysis. The authors point out that for years he was a typical infantile giant, and remained infantile as far as the extremities were concerned, as they continued to grow until death, while during the last few years of his life the head assumed characteristic acromegalic characters.

Such a transformation was also discernible in the giant Simon Botis, reported by Buday and Jansco in the greatest detail as to measurements and post-mortem findings. He measured 198 cm. at 35 years and 202 cm. when he died at 37 years. His sexual function was very active at 17 years, but impotence set in at 20. He then measured 163 cm. and began to grow rapidly. Some years later acromegalic changes in the

head appeared. The sella and hypophysis were greatly enlarged. The testicles were atrophic. Most of the viscera were very large. The small intestine measured 30.7 meters, the large 3.8 meters.

Still more noteworthy is the "acromegalization" of a giantess ("Lady Aama"), only 17 years old at death, reported by Woods Hutchinson. Scarcely one-third of the epiphyses were united and the extremities were very long in proportion to the short trunk. The mammary glands were almost absent; in fact, there was nothing in her appearance above the pubes to indicate her sex. The lower jaw, nose, frontal sinuses and the hands were unduly prominent. At necropsy the uterus and ovaries were found to be extremely small, the vagina and labiæ also small, but the clitoris was very large and resembled a small penis. The sella and hypophysis were enlarged.

Fig. 14. The Portuguese Giant, Lopez. (Lemos.)

Two cases related by Kienböck may be included. Case 1 was that of one of the giant guardsmen who accompanied Emperor William to Rome in 1903. He did not mature sexually until 21 years old, though his genitals were of normal size and he later developed good sexual power. The growth of beard and pubic hairs was scant. When studied at 27 his lower jaw, malar bones, and frontal sinuses had become large, but the sella was normal. His height was 202 cm. Case 2 was that of a woman of 27 years, 200 cm. tall, who never had menstruated. The breasts were undeveloped. She had previously been slender and good looking, but now acromegalic signs were marked and the sella enlarged.

The oldest giant on record, a man of 76 years, bent, 189 cm. tall, but over 2 meters if straightened up, reported by Sarteschi, had infantile genitalia as well as acromegalic facies and extremities.

A combination of gigantism, infantilism, feminism and acromegaly existed in the case of Louis R., who died at 27 years, and whose skeleton is most thoroughly described by R. Verneau. He was 214 cm. tall. His muscular strength was poor, but he could eat and drink enormous quantities. His build was asymmetrical and his friends maintained that he grew on one side at a time, so he sometimes was inclined to the right and

Fig. 15. Hand of Portuguese Giant, Lopez, compared with the normal. (Lemos.)

Fig. 16. Foot of the Portuguese Giant, Lopez, compared with the normal. (Lemos.)

sometimes to the left. Unlike most giants his extremities were relatively short and the proximal segments were relatively shorter than the distal. The clavicles were unusually long. He was beardless. Remains of the epiphyseal lines were still visible and there was delayed ossification of the vertebral cartilages. The pelvis and the sternum were distinctly feminine. The sella turcica, the accessory sinuses and the lower jaw

Fig. 17. Röntgenogram of hand of the Portuguese Giant, Lopez. (Lemos.)

were greatly enlarged, providing the acromegalic features in the case. The hands and feet were not disproportionate.

An acromegalic circus giant, 8 feet 10 inches tall, and 40 years old at the time of his death from diphtheria, is reported, with postmortem examination, by D. Symmers. His brother was also an acromegalic giant. The acromegaly in the patient was obvious: he showed marked prognathism, enormous hands and feet, and enlarged sella containing a hypophyseal adenoma. There were also signs of infantilism: absence of beard; scanty pubic and axillary hair; small penis, prostate and testicles; persistent thymus and small aorta. The thyroid was large.

An excellent example of gigantism and infantilism with acromegalic features is the Portuguese giant, Jose Lopez, 21 years old, 210 cm. (6 ft. 11 in.) tall, weight 117 kilograms, reported by Magalhaes Lemos. His birth was normal. As a child he suffered from severe headaches, and he claims never to have had any vision in his left eye. After smallpox at six or seven years his rapid growth attracted attention and it continued to be rapid until the age of 12 years. When examined at the age of 21 it was striking that his legs and particularly the feet were disproportionately long (36 cm.), as were his arms and hands. The facial part of the head was relatively large, the lips thick, the nose broad and the tongue large. The genitalia were decidedly rudimentary and there was neither axillary nor pubic hair. The muscular power was poor and the tendon reflexes were feeble. The eyes showed congenital optic atrophy in the left eye with blindness, a temporal scotoma in the right eye and paresis of both external recti. Röntgenologic examination showed open epiphyseal lines at the lower end of the radius and ulna. Mentally he was dull, melancholy and timid. The thyroid gland was palpable, but small.

Lemos considers this giant as an instance of Brissaud's type of infantilism on account of his undeveloped genitalia and absence of puberty while the features of the Lorain type were lacking.

Gigantism in Childhood

The reported cases in children who at a given age have reached an altogether abnormal size, sometimes associated with precocious mental and sexual development, must be considered apart from gigantism proper. They are very dissimilar, and while some of them recall stages in the development of true giants, others are instances of precocious growth dependent on serious disorders incompatible with prolongation of life beyond childhood.

A very distinct group is that associated with *adrenal tumors.* Linser describes a boy, 5½ years old, 138 cm. tall, who began to grow rapidly and develop an abnormal growth of hair at four years. The penis and testicles were large, the former 9 cm. long, and erections occurred. The prostate was of a size normal at 15 years. Death followed attempted removal of a palpable tumor in the region of the left kidney. It proved to be hypernephroma of the left adrenal. The pituitary and pineal bodies were normal macroscopically and microscopically. Jump, Beates and Babcock record the case of a girl of seven years on whom axillary and pubic hair appeared at the age of one year. At seven years she measured 53 inches in length and weighed 90 lbs. Growth of beard had appeared, and the clitoris was enlarged. A tumor in the right hypochondriac region ap-

peared, which at necropsy proved to be hypernephroma. The hypophysis was normal. These authors state that up to the time of their report (1914) seventeen such cases with necropsy had been recorded, and that all cases were alike. There was a tendency to development of male characteristics in girls and to an exaggeration of male characteristics in boys. All had died before the age of sixteen years.

Fig. 18. Precocious boy of six years beside normal boy of fifteen years. (After Hudovernig and Popovits.)

To the *sexual glands* we relate Sacchi's case of a child 143 cm. tall at nine years with a testicular tumor and to the *sexual glands and hypophysis* Neurath's (*b*) "Fettkinder," which were both abnormally tall and abnormally fat.

The *pineal gland* was the seat of a "psammosarcoma cysticum" in the well-known case of Œstreich and Slawyk. A boy, normal up to the age of three years, then began to grow rapidly, measuring 108 cm. at four years. The bones and muscles were strongly developed. The penis was 9 cm. long, the pubic hair 1 cm. long, and the mammæ hypertrophic. Choked disc and convulsions pointed to the presence of a brain tumor which was found to occupy part of the third ventricle and to have originated in the pineal body. The thyroid, thymus, and hypophysis were normal. A similar case is reported by Frankl-Hochwart in a boy of five years, whose size would have been normal in a boy of nine years.

A possible *acromegalic type* is briefly related by de Monchy in a child 17 months old and 93 cm. (36½ in.) in length, with ocular signs of increased intracranial pressure. The hands and feet were abnormally large, and röntgenologic examination revealed that the frontal sinuses were developed at this unusually early age, but there was no definite proof of sellar enlargement.

Unclassifiable (*polyglandular?*) *Cases.*—A remarkable case was reported in 1903 by Hudovernig and Popovits and three years later by

Hudovernig. This boy at the time of the first report was 5¾ years old, measured 137 cm. and weighed 35.5 kg. The genitalia were of adult size. When he sat on a woman's lap erections had been observed. The ossification of the metacarpal bones was nearly completed. He was backward mentally. Thyroid treatment gave no results but, curiously enough, he improved both mentally and physically on ovarian substance. The testicles actually decreased in size!

Anton relates the following case: A female child of normal ancestry and normal early infancy developed very rapidly. She walked and talked at one year. Menstruation began at three years, lasted three to four days, but occurred only twice a year. When examined at six years of age she had the appearance of a girl in the 'teens, was 140 cm. tall (4 ft. 8 in.) and had well developed breasts, broadened hips, and pubic and axillary hair. She was also precocious mentally. The sella was moderately enlarged, but vision and the eye grounds were normal. At nine years she measured 150 cm., the blood pressure was 85 mm., and the blood showed relative increase in lymphocytes. The thyroid was moderately enlarged. No thymus shadow could be made out.

Fig. 19. Anterior and posterior view of precocious girl of six years. (After Anton, Monatsschrift. f. Psych. u. Neurol.)

Sanz's case is unique, showing features of gigantism, acromegaly and pseudohypertrophic muscular dystrophy in a boy of 11 years, 170 cm. tall. Prognathism was extreme, and the nose prominent.

"Giant infants" are now and then recorded, but not in sufficient detail. Thus Hastings Gilford relates the case of a Welsh boy, of usual size at birth, who began to grow very rapidly at the age of nine months. When he was examined at 13 months he was 91 cm. long and weighed 27 kilograms. There was a tremendous overgrowth of subcutaneous fat, but his muscles were exceedingly well developed and he seemed as strong as the average child of 8 or 9 years. He died a month later, supposedly of a

syncopal attack dependent on status lymphaticus. (This recalls Neurath's cases.)

Wilson describes the case of the fifth child of normal parents who was of usual size at birth, but at six weeks he began to grow very rapidly.

Fig. 20. Röntgenogram of hand of precocious girl of six years in center. To left and right are the hands of myxedematous dwarfs, 13 and 23 years old. (After Anton, Monatsschrift. f. Psych. u. Neurol.)

At nine months he measured 3 feet 1¼ inches in length and was well proportioned. He measured 22¾ in. around the chest and 24 in. around the small of the back and his thigh was 18 in. in circumference.

Heredity in Gigantism

Considering the rarity of gigantism the comparatively frequent occurrence of more than one case in a family is striking. In some families so many individuals have been abnormally large that this trait must be considered dominant, as in the case of the last example of gigantism and infantilism related in this article. De Neuville states that the English giant, Robert Hales, born in 1820, himself 7 feet 6 inches tall, was the son of a father of 6 feet 6 inches and mother of 6 feet. An ancestor who

lived at the time of Henry VIII had measured 8 feet 8 inches. Five sisters had an average height of 6 feet 3 inches, the tallest who measured 7 feet 2 inches having died at twenty. Four brothers averaged 6 feet 6 inches. The same author says of one Louis Frenz, 7 feet 6 inches tall, born in 1800, that he had one sister "nearly as tall" and a brother "still taller" than himself.

According to Meige the Chinese giant Chang, 8 feet tall, had a sister of 8 feet 4 inches. Among the cases we have related on the previous pages there are many similar data: Launois and Roy's giant Charles had an uncle 200 cm. tall. Achard and Loeper's "Tambourmajor" had a father of 195 cm. and a paternal uncle of 210 cm. Both the father and grandfather of Jödiche's giant were of giant size, as was the brother of the one described by Symmers, and the uncle of the giant Constantin.

However, as was long ago emphasized by Woods Hutchinson, the great majority of giants have been sterile, and all attempts at breeding giants have been futile. One giant couple, however, called by Gould and Pyle "the tallest married couple known to mankind," Captain Bates of Kentucky, 7 feet 1 inch, and his wife, the Nova Scotia giantess, Anna Swann, 7 feet 9 inches, had born to them (according to Gilford) a child which weighed 23¾ lbs. and measured 30 inches in length. It died during delivery, "as no forceps could be procured of sufficient size to grasp the head." This was their second child, the first one having weighed 19 lbs.

Association of Gigantism with Other Abnormalities.—We may begin with the biblical account of Goliath's son with six fingers and six toes. R. C. Lucas describes a family in which there were many individuals with six fingers and toes and one of the ancestors was said to have been exhibited as a giantess. Several members of this family also had webbed supernumerary digits and two were afflicted with harelip. It is interesting that Bertolotti sees a relationship between the hypophysis and polydactylism.

Gould and Pyle mention a German giantess who lived during the time of Queen Anne and had neither hands nor feet.

Ballistini describes syndactylism of the second and third toes of both feet in a young acromegalic giant. Sanz describes a boy of eleven years, 170 cm. tall, with prognathism, prominent nose, and pseudohypertrophic muscular dystrophy. The association with leontiasis ossea has already been alluded to.

Metabolism in Gigantism.—Apparently the first and only thorough investigation of metabolism in a case of gigantism was made by Levi and Franchini on the giant Palozzi, whose case is related on page 170. They found that the results were similar to those obtained in acromegaly. Previously, Launois and Roy had shown in the giant Charles an increased daily amount of urine with increased elimination of chlorides, phosphates and urea. Sugar had been found in the urine of the giant Botis by Buday

and Jansco, and in the acromegalic giant of Achard and Loeper. Franchini had previously made similar studies in several cases of acromegaly and the results in the two conditions are tabulated as follows:

Acromegaly.	*Gigantism.*
In general good absorption of nitrogen and fat by the digestive apparatus. Strong retention of the two substances.	Same results.
In half of the cases there was alteration in the different nitrogen groups with insufficiency of urea and increase of ammonia and amino acids.	Same alterations and increase in the precipitable nitrogen.
Altered splitting of the fats with increase in neutral fats and cholesterin and increased elimination of fatty acids and soaps.	Less accentuated loss of soaps and less evident increase in neutral fats; notable insufficiency in fatty acids and considerable increase in cholesterin.
Marked elimination of phosphorus, especially in the periods of exacerbation of the disease and in some cases inversion of the phosphatic formula.	Nearly normal elimination of phosphorus and increase in the earthy phosphates.
No alteration in the relation between neutral sulphur and acid sulphur and consequently no alteration in the oxidative processes.	Increase in neutral sulphur over acid sulphur.
In one-third of the cases increase in the sulphuric ethers, and in nearly all cases notable increase in indican, skatol and phenol.	Increase in sulphuric ethers and in skatol, phenol and particularly indican.
Retention of calcium more frequent than its loss, but the variation from day to day is remarkable.	Slight retention of calcium.
Retention of magnesium constant in all cases.	Not investigated.

Localized Giant Growth. Hemihypertrophy

It is not within the scope of this article, which deals primarily with growth disturbances of endocrin origin, to discuss the innumerable varieties of malformations in which localized overgrowth of certain parts has taken place. They are largely referable to amniotic adhesions and other accidental disturbances during fetal life, but in some instances we must assume a *vitium primæ formationis*, back of which there may be endocrin factors. There are transitional forms between cases of quite general congenital overgrowth of the extremities, like that of Salle, which we have discussed in the chapter on acromegaly, and the more localized ones. Among well studied cases are that of Busch of enlargement of the left foot, with huge deposits of fat; that of Widenmann of enlargement of the right leg, beginning at the age of six years, associated with cryptorchidism, nevi, and exophthalmos; Max Hofmann's case of enlarged right foot in connection with which the question of congenital acromegaly is raised. As an example of this kind we will relate the following case: Wieland describes in great detail the features of the congenitally hypertrophic left foot of a male child, otherwise normal and of good heredity, who was observed from the time of birth. Even then the hypertrophic distal part of the foot was sharply defined from the proximal normal part. Later this line of demarcation developed into a deep furrow. The big toe was of enormous size and the fused second and third toes were equally large, while the fourth and fifth were of normal size. At the age of eight months the enlarged part suddenly began to grow and reached almost double size in a month. Two months later a similar sudden growth took place and amputation was performed. Histologic examination led to the conclusion that there was a genuine hypertrophy and hyperplasia of all tissue elements in the affected portion and the most active overgrowth had taken place in the adipose tissue. Only the skin and muscles were atrophic. The bones showed both hyperplastic and regressive changes. On account of the peculiar combination of hyperplastic and regressive changes the author proposes to designate this type as the dystrophic form of partial giant-growth.

He admits that the presence of a distinct line of demarcation between the hyperplastic and the normal parts in his case and those of Busch, Friedberg and others suggest amniotic bands, but he believes that the skeletal changes are not explained on this theory. He believes that there must be a specific *vitium primæ formationis:* in other words, a faulty anlage.

Hemihypertrophy

Unilateral hypertrophy is a congenital malformation which gives to the victim the appearance of possessing a body with the lateral halves belonging to two different persons not of the same size. Superficially, the appearance suggests unilateral acromegaly, but symptoms of hypophysis tumor or any other progressive brain lesion are lacking. There are no

Fig. 21. Hemihypertrophy. (After Bassoe, Am. J. Insan.)

eye symptoms, and the sella turcica is not enlarged. The early literature is fully reviewed by Trélat and Monod, and later reviews with reports of new cases are contributed among others by Arnheim, Cagiati, Bassoe, and Stier. Heredity plays no rôle. The male sex and the right side seem to predominate. The hypertrophy mainly involves the tissues of mesoblastic origin, namely, the subcutaneous tissues, muscle, and bone. Nevi and pigmentation of the skin are usually present on the hypertrophic side. Postmortem examinations have not thrown any light on the underlying

cause. Stier has collected a large number of cases of hemihypertrophy and hemiatrophy, general and local, and of supernumerary nipples, fingers and toes, etc., and has noted whether the persons concerned were right-handed or left-handed. He is convinced that the excess formations, such as hemihypertrophy and supernumerary digits, more often occur on the right side in right-handed individuals, while hemiatrophies and defect

Fig. 22. Hemihypertrophy. (After Bassoe, Am. J. Insan.)

malformations are more frequent on the left side. In other words, there seems to be some relationship between these malformations and the dominant cerebral hemisphere, but the mechanism by which they are produced remains unknown.

Naturally cases of this kind are sometimes recorded as instances of unilateral acromegaly, a non-existent condition. This title was chosen by Burchardt, who briefly describes a girl eleven years old whose left eye, ear and whole face, as well as the left hand and foot, were larger than the right. The left leg, however, was shorter than the right.

Two cases in the literature may be designated "alternating" hemihypertrophy, in analogy with the "alternating hemiplegia" of a pons lesion, namely, those of Reissmann and Behan, in which the face was enlarged on one side, the arm and leg on the other. Other malformations, such as syndactylism, enlargement of one or two digits, and undescended testicle have sometimes been associated.

From the above it may be concluded that hemihypertrophy, whatever its ultimate cause and its mechanism may be, is a teratologic problem of radically different pathogenesis than general gigantism.

Dwarfism . . . . . ***Peter Bassoe***

Classification—Proportionate Dwarfs—Disproportionte Dwarfs—Primordial Dwarfism—Hypophyseal Dwarfism—Other Endocrine Disorders Leading to General Dwarfism—False or Disproportionate Dwarfs—Chondrodystrophia Fetalis.

Dwarfism

PETER BASSOE

CHICAGO

A dwarf is a person of very small size as compared with the average of individuals of the same age and race (Meige).

The term is applied both to those who owe their defective stature to local deformity and to those who are not deformed, but merely below the level of normal growth, say of 150 cm. in the white race (Gilford). To Meige's definition Levi adds that true dwarfs must present the somatic characters and functions, particularly sexual, corresponding to their age. This restriction is made so as to exclude the subjects of infantilism, a disorder characterized by persistence of somatic and psychic characteristics belonging to a much lower age than the actual one of the individual under consideration. We have seen before that subjects of infantilism may be of normal or even gigantic size. Yet the immaturity common to all of them irrespective of size is so conspicuous that they should be considered in a class by themselves, regardless of size.

Taking the term dwarf in its literal sense the following classification adopted after von Hansemann appears appropriate:

I. Proportionate Dwarfs.
- A. *Primordial or true dwarfs.* (*Essential Microsomia.*)
- B. *Hypophyseal dwarfs.* (*Paltauf type.*)
- C. *Intermediate or mixed forms.*

II. Disproportionate Dwarfs
- A. *Achondroplasia.* (*Chondrodystrophia fœtalis.*)
- B. *Rachitic dwarfs.*
- C. *Cretins.*
- D. *Congenital syphilis.*

Primordial Dwarfism. (*Essential Microsomia.*)—The best description of this condition is given by Ettore Levi (*c*). This kind of dwarf is a perfectly normal human being, physically and mentally, merely of small size, or, as Meige puts it, a normal person viewed through the large end of a telescope. There are no features of infantilism, either physical or psychic. Genital development and function are normal, and ossification occurs at normal age. The condition is a familial one, more frequent in

the males and transmitted through the father (Levi). There is no evidence of endocrin disorder. Röntgenologically the sella turcica is normal. These dwarfs, unlike the hypophyseal ones, are small at birth. As an example we will select Case III in Levi's article as he considers this one particularly typical.

This little man (Fig. 2) was 33 years old, measured 111 cm. (43½ inches) and weighed 25 kg. His mother and his four grandparents had been of normal size and enjoyed excellent health, while his father was a dwarf of the same size as the patient. Five brothers were of normal size and no cases of dwarfism, other than the father, were known either in the family or in the vicinity. Unlike most cases of this class, the patient was said not to have been very small at birth. He walked and talked early, and dentition was normal. He practically ceased to grow between the ages of eight and ten years but normal puberty was attained at fifteen. Except for his size he was normal in every way. Levi gives detailed measurements and a full description of the examination of his organs and their function, everything being found to be normal. This dwarf married a woman of normal size. Levi describes their first child, a girl of 22 months who weighed 2 kilograms at birth and at the time of observation was of the size of a normal child of one year. She was healthy, well proportioned, and resembled the father closely. Levi believes she will remain a dwarf.

Fig. 1. Essential dwarfism. After E. Levi, Nouv. Iconogr. de la Salpêtrière, 1910.

To the primordial dwarfs undoubtedly belong many of the famous dwarfs of circuses and museums, such as "General Tom Thumb"; his wife, Lavinia Warren, and their companion "Commodore Nutt." The principal data regarding them and other "professional" dwarfs have been compiled by Hastings Gilford in his book. Most of the dwarfs described by him as instances of "sexual ateleiosis" (dwarfs with normal sexual development) probably belong here, while under the head of "asexual ateleiosis" he describes Paltauf's case and others preferably placed in the group of hypophyseal dwarfism. Gilford rather minimizes the rôle of the demonstrable disorders of the

hypophysis and of other ductless glands which he considers as merely part of a disorder of the nature of a "discontinuous variation" of the human species viewed from an anthropological standpoint, rather than as actual causes of the growth disturbance.

Hypophyseal Dwarfism.—The first accurate description of dwarfs of this class was made by Paltauf in 1891, and hence they are often known as "Paltauf dwarfs." They are of normal size at birth but in later childhood lag behind and soon their growth becomes almost imperceptible. However, as the epiphyseal lines remain open even to old age a slight growth continues. Thus, a dwarf observed by Joachimsthal was 106 cm. tall at 22 years and 128 cm. at 36 years. Peritz (*c*) believes that the "inherent growth tendency" existing at birth causes a person to reach a height of 130–140 cm. but to get beyond this hypophyseal activity is necessary. He considers this form of dwarfism the purest type of "formal infantilism." In addition to the persistence of the epiphyseal lines there is failure of genital development, and psychic infantilism also may be present. These dwarfs remain children in body and mind and never develop true adult characteristics but they often live long enough to acquire senile features. The latter may appear very early, even in infancy or childhood, the combination of infantilism and senilism being designated "Progeria" by Gilford. The skin is particularly liable to assume a senile appearance at a relatively early age (geroderma). Necropsies have shown destructive lesions of the hypophysis, particularly its anterior lobe. Erdheim points out that hypophyseal dwarfism results from a pure intrasellar lesion while associated lesions of the base of the brain in cases of tumors growing beyond the sella cause the additional feature of adipositas cerebralis to be present. Hence the relationship to the Fröhlich syndrome is a close one, and there are cases possessing the features of both conditions, such as the one reported by A. W. Hewlett. This patient (Fig. 3) was a man 27 years old, 4 feet 9½ inches (146 cm.) tall and weighing 166½ pounds. He was very obese, blind from optic atrophy, sexually infantile, and had diabetes insipidus. He had no beard, and the mentality was childish. A woman, 27 years old, obese, 121 cm. tall, proportionate, and said to have grown 6 cm. after the age of 23 years is reported by E. J. Kraus. She never menstruated and was an idiot. Necropsy revealed an exceedingly small hypophysis (0.16

Fig. 2. Essential dwarfism. After Levi, Nouv. Iconogr. de la Salpêtrière, 1910.

gm.) and thyroid (6 gm.). The brain weighed 1,038 gm. and showed microgyria as well as hypoplasia of the right hemisphere.

Cases of Hypophyseal Dwarfism.—The first really thoroughly studied case is that reported by Erdheim. The patient was a man, 38 years old, 142 cm. (56 inches) tall, with open epiphyseal lines, cryptorchidism, small penis, and absence of beard, pubic and axillary hair. The anatomic de-

Fig. 3. Adipose hypophyseal dwarf. After Hewlett, Archives Int. Med., vol. 9.

scription and the analysis of the case are most thorough and interesting. The sella turcica was enlarged and contained a cystic mixed tumor of the hypophysis, hence a destructive lesion. The histologic changes in the open epiphyses are described in the greatest detail.

In 1920, the case of a man 91 years old and 132 cm. (52 inches) tall, was reported by A. Priesel. He had been of normal size as a child and his growth practically ceased at the age of 15 years. He was normal mentally. His voice had been rather high pitched. The clinical data are meager, probably because he came under observation only as an old

man. The postmortem findings, however, are related in great detail, with measurements of every bone and organ in the body. The extremities were of proportionate length. The thyroid and adrenals were very small, the genitalia small and the parathyroids unusually small. The hypophysis was attached to the brain by an infundibulum only 0.5 mm. thick. The posterior lobe was not within the sella turcica but was lying at the base of the brain, below and behind the chiasma. A thin layer of glandular tissue connected it with the intrasellar portion of the gland which was converted into a thin-walled cyst. There was also another cyst which was found to represent a dilatation of the persistent craniopharyngeal duct. It is obvious, therefore, that a decided congenital malformation of the hypophysis was present as well as extensive destruction of its glandular elements. On acount of these malformations the normally close connection between the anterior or glandular and the posterior or neural lobes of the gland did not exist. Unlike most other cases of hypophyseal dwarfism, a true tumor growth was not present. In this respect the case resembles one reported by Simmonds in which the atrophy and cyst formation of the anterior lobe were attributed to an embolic process. All the epiphyseal lines were found to be closed in Priesel's case, not surprising in view of the advanced age. The genitalia were atrophic, yet infantile.

A case of dwarfism attributed chiefly to general infantilism is reported by C. Sternberg. His patient was a boy 17 years old and 92 cm. (36¼ inches) tall. There were no cases of anomalies of growth in the family. He was said to have been of normal size at birth but curvature of the spine and partial inhibition of growth were present from the age of a year and a half. His intelligence was good. The cause of death was tuberculous spondylitis. In spite of the resulting deformity of the back, the case very properly is classified as one of true dwarfism rather than of the false, disproportionate variety purely dependent on Pott's disease. The other bones were normal and all the epiphyseal lines wide open. The appearance of the body was decidedly infantile. The genitalia were small and there was no trace of beard, axillary or pubic hair. The thyroid, adrenals and hypophysis were abnormally small. The latter, however, as well as the adrenals were histologically normal. The thyroid also showed little histologic change. The testicles showed changes which were interpreted as due to defective development rather than to atrophy. This fact, that the testicles were not atrophic but showed primary defect of development, is interpreted in the sense that the dwarfism cannot be attributed to hypophyseal deficiency which would have caused atrophy of the testicles. The condition is looked upon as one of dwarfism due to general infantilism and the group to which it belongs may be designated as hypoplastic dwarfism. This author described also a boy 20 years old, 126 cm. (49¾ inches) tall, well proportioned but mentally defective and with definite thyroid deficiency while the hypophysis was nor-

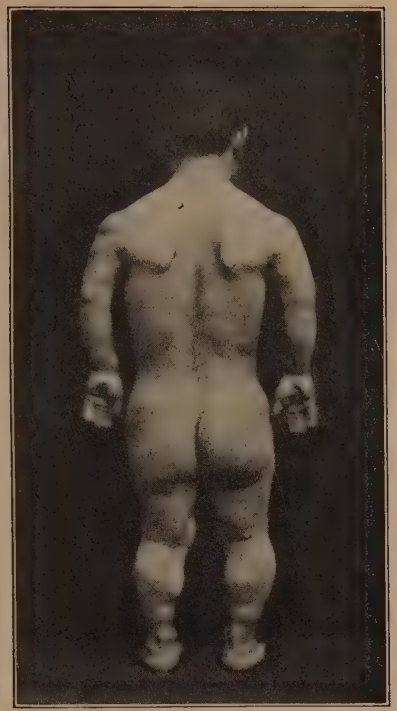
mal. The genitalia were infantile. The case is looked upon as principally of thyroid origin but on account of the proportionate growth it belongs to true dwarfism and not to the disproportionate or false dwarfism associated with ordinary cretinism. The conclusion of the author is that in addition to hypophyseal dwarfism there are rare cases of true dwarfism due to general infantilism and to thyroid deficiency.

Margarete Levy relates the case of a woman, 44 years old, whose parents were normal but a cousin was a dwarf. The patient was of normal size until the age of 4 years. After that she scarcely grew and she only reached a height of 103 cm. (40½ inches). Her weight was 51 pounds. She had never menstruated. There was no axillary or pubic hair and the breasts were undeveloped. The skin was cold and dry and she never perspired. The thyroid was not palpable. The mental development was normal. Röntgenologic examination of the extremities showed open epiphyseal lines. The sella turcica was not enlarged and the skull was normal otherwise. Alimentary glycosuria was produced by the ingestion of 100 grams of glucose.

Two cases, undoubtedly of endocrin origin, though not proportionate, are worthy of mention. One, that of a man, 22 years old, 142 cm. (56 inches) tall, weight 27 kilograms, with disproportionately long extremities, is reported by J. Bauer. The testicles were not palpable, the penis was small, trunk devoid of hair, the voice high-pitched. The thymus was enlarged, the sella turcica abnormally small. The long limbs were attributed to the eunuchoid condition. Van der Scheer described a female imbecile dwarf of 32 years, with certain acromegalic features, namely a large tongue, prominent lower jaw and accentuated secondary sexual characteristics, while the internal genitalia were poorly developed and the menstruation, which was scanty and irregular, first appeared at 26 years. The extremities which were of normal proportion at birth later became abnormally small but chondrodystrophia could be excluded, partly on account of the normal condition at birth. The Wassermann test was positive and there were scars about the anus so congenital syphilis undoubtedly played a part. The sella turcica was of normal size, and the epiphyseal lines were closed.

Other Endocrin Disorders Leading to General Dwarfism.—In other parts of this work it is pointed out that dwarfism occurs as a feature of infantilism and cretinism, and that the thyroid, thymus and other ductless glands play a part. To avoid repetition these conditions will not be taken up in this chapter.

False or Disproportionate Dwarfs.—A great many conditions in infancy and childhood lead to stunting of growth of more or less disproportionate character. Rickets, Pott's disease, and congenital syphilis are the more common causes. These types of dwarfism do not come within the scope of the present work.



Figs. 4, 5, 6. Achondroplasia. After Levi.

Chondrodystrophia Fetalis. (*Achondroplasia*).—This curious condition of micromelic or short-limbed dwarfism is as clear cut and uniform clinically as its etiology is obscure. The chief features are: 1. Short arms and legs. 2. Trunk of normal size. 3 Relatively large and brachycephalic head. These features exist at birth, in fact they are present early in fetal life. The condition is frequently hereditary and familial. The muscular system is strongly developed, hence these dwarfs frequently distinguish themselves as athletes and acrobats. It is thought that the dwarf gladiators of the Roman emperor Domitian were of this variety as their statues which still exist represent them with the typical short extremities (Wagner). Their mentality is usually good. Among other rather constant features are a deep insertion of the nose with anteroposterior shortening of the base of the skull due to the small size of the "os tribasilare," lumbar lordosis, and abnormal shortness of the fourth fingers and toes. The latter feature particularly has been emphasized by E. Levi (*b*). The enlargement of the head in these dwarfs has recently been studied by W. E. Dandy and attributed by him to slight and stationary hydrocephalus.

G. A. Wagner emphasizes the tendency to early and excessive development of the genital organs and their function—a veritable hypergenitalism. To the latter he ascribes an important and primary rôle in the etiology of the condition. He presents the contrast between eunuchs and chondrodystrophic dwarfs as follows:

EUNUCHS	CHONDRODYSTROPHIC DWARFS
Skull dolichocephalic.	Skull brachycephalic.
Increased growth in length of the extremities.	Abnormally short extremities.
Epiphyseal lines remain open abnormally long.	Frequently premature closure of the epiphyses.

Wagner is not certain whether the bony growth is directly modified by the excessive gonad activity or through interaction by other endocrin glands. The hypergenitalism is thought to cause the excessive muscle activity which in turn is an important factor in inhibiting growth in length. A similar theory of gonad overactivity has previously been suggested by others (Parhon, Shunda and Zalplachta).

Less plausible is the theory assigning the main rôle to the hypophysis, which has been advanced, among others, by Baumel and Margarot, who were much impressed by the adiposity of a patient described by them.

All endocrin theories of this condition, however, are denied by many observers. Osteochondritis in early fetal life from toxic-infectious causes (Porak and Durante), faulty mechanical conditions causing pressure on

Figs. 7, 8, 9. Achondroplasia. After Baumel and Margarot.

Figs. 10, 11. Achondroplasia, showing short fourth fingers and toes. After Levi.

the fetus (Wiesermann), and primary malformations of the epiphyseal cartilages (Kaufmann (*a*) (*b*)) so far have received more favorable attention as possible causes.

(A complete account of all cases of dwarfism and an abstract of the entire literature up to 1912, together with plates reproducing practically all available illustrations, and a huge bibliography are found in the article by Rischbieth and Barrington.)

Infantilism . . . . . *August Strauch*

Introduction—The Essential Nature of Infantilism—Infantilism in Its General Aspects—General Infantilism—Types of Infantilism—Classification—Infantilism Due to True Ductless Glandular Diseases—Dystrophic Infantalism with the Following Varieties—Discussion of Various Types of Infantilism—Myxinfantilism—Dysgenital Infantilism—Nanosomonia of Hypophysial Origin—Hypophysial Infantilism—Multiglandular Infantilism—Dystrophic Infantilism—Etiology and Pathogenesis—Dystrophic Infantilism in Status Thymicolymphaticus—Infantilism Due to Heart Lesions—Infantilism Resulting from Chronic Intoxications and Infections—General Syphilidotoxic Dystrophies—Intestinal and Pancreatic Infantilism—Varieties of Dystrophic Infantilism in Hepatic and Renal Diseases—Infantilism Resulting from Brain Lesions; Traumas—Infantilism Due to Unhygienic Surroundings and Malnutrition—Progerio as a Manifestation of Infantilism—Psychic Infantilism—Treatment of Infantilism.

Infantilism

AUGUST STRAUCH

CHICAGO

Introduction

The Essential Nature of Infantilism.—During the entire evolutionary time from the embryonic stage to the full development of postnatal life, developmental disturbances can occur whereby either the whole body or single organs retain the forms and especially the size or other qualities that normally belong to a transitional stage of evolution. For the designation of the persistence of childish characteristics into the adult life, physical as well as psychical, Lasègue has coined the term Infantilism. This simple and general definition allows a wide range of application; with the increasing knowledge and understanding of various clinical pictures it underwent modifications, being circumscribed by different authors in varying ways, by Anton, Peritz and the French, perhaps with the widest limits. Though a definite differentiation from a number of related or similar pathologic conditions has at the present not yet met with general acceptance, and though the various attempts to make subdivisions of this anomaly are not free from objections, much progress has been made in elucidating this highly fascinating subject that is one of the most fruitful in the domain of medical research.

We speak of a partial and a universal infantilism. Partial infantilism signifies the abnormal persistence of one organ, or organ system, or its part in a stage of development that normally is only temporary; when such a stoppage of evolution begins during the intra-uterine life, some authors speak of embryonalism or fetalism, as for instance in the case of the persistence of an open foramen ovale, coloboma of the eye, cleft-palate and the various congenital fissures of the face. Tandler distinguishes a formal and topic form of infantilism (embryonalism) depending on whether the form and size or the location of the organ remains infantile. The first type is exemplified by micrognathy, small cartilaginous larynx with a high pitched voice, an infantile pug nose in the adult of those races who normally have straight or convex noses; the retention of infantile proportions of the skeleton or its parts, a cecum that tapers off gradually to the appendix, a disproportionately long flexure of the sigmoid

with a broad mesentery; superficial lobulation of the kidneys, small testicles, small, infantile uterus or ovaries, the persistence of markedly convoluted tubes and a hypoplastic circulatory system.

Paradigms of topical infantilism are a left-sided cecum due to failure of complete rotations of the mesenterium commune during the intrauterine life, congenital enteroptosis, certain dystopias of the kidneys, due to retention into later life of their original position in the pelvis, cryptorchidism or incompleted descent of the testes. Defects of growth of hair, as absence of beard or pubic crines or hair on the rest of the body in the male with otherwise good physical proportions and also pure psychic infantilism are examples of partial infantilism.

As seen, a number of instances are identical with hypoplasias of the organs concerned. While some instances of partial infantilism have principally an anatomical but no clinical significance, others, as the partial defects of the genital or the thyroid glands, will not remain local but exert momentous effects upon the function of other organs and upon the development and integrity of the entire organism. Thus well characteristic clinical pictures of general infantilism will develop.

Infantilism in Its General Aspects

General infantilism is a disturbance of the development in which the whole organism retains its infantile type somatically as well as psychically, thus not obtaining the full characters of the adult of his species; it is the arrest or delay in development of the entire organism during the progressive stage. In the phrase of Tandler it is a morphologic anachronism. In the strict sense the term should be used only after the termination of childhood; however, it is applied also to the early life, having then only a relative meaning, of course, namely, designating the persistence in size and transitory characteristics of an earlier period of development. To be sure, it may be difficult or impossible to determine whether the standstill during a certain period of childhood will be permanent or whether the child will make up for the retardation of development later, as is often the case. In the strict sense also, universal infantilism is only partial and we cannot expect to find a complete congruency or identity in the organs, their functions, the proportions of all parts, the metabolism and the psychic activities with those of infancy or childhood. The principal characteristics of the latter are the faculty of growth, depending upon the non-closure of the epiphyses, a head large in proportion to the rest of the body, comparatively short legs, especially during the first year of life, lack of function of the genitalia, and certain psychic qualities marked by immaturity. The principal features of infantilism enumerated are smallness of stature due to delay or arrest of the growth of the skeleton,

delay of ossification with persistence of the epiphysial discs, underdevelopment of the musculature and a corresponding smallness of the organs, especially faulty development of the sexual apparatus, the secondary sexual characters and the vita sexualis; and finally the persistence of the psychic attributes in the childhood stage. This premature stoppage of development shows also a tendency to end in premature degeneration with increased liability to premature senility.

Infantilism is of great pathogenetic importance. Due to the constitutional inferiority of the whole organism or certain parts even the normal demands of daily life overtax the functional capacity of the individual who suffers much under the rough influences of life and is liable to succumb prematurely in the struggle for existence. The lowered resistance of the cells not only facilitates infections but renders their prognosis more grave than in the normal individuals. Thus the majority die young and tuberculosis especially reaps a rich harvest among them. In addition, mechanical conditions with or without a local tissue inferiority may create a locus minoris resistentiæ, predisposing to serious disturbances. Thus the so-called asthenic thorax with stenosis of the upper aperture, as result of developmental inhibition invites apical tuberculosis, and very tortuous, infantile Fallopian tubes predispose to extension of a gonorrheal infection and the aggravation of its severity. The fertilized ovum on its transport is liable to be retained in one of the tubal loculamenta, finding there a nidus with the result of tubal pregnancy and its complications. An infantile uterus causes sterility and an abdominal testicle has a tendency to undergo malignant degeneration. The whole sexual life of a decidedly infantile woman is, as W. A. Freund has characterized it, subject to a great many troubles. "Even the development at puberty is difficult; the menstruation has a tardy onset, is often scanty, ceases for months or even years with chlorotic manifestations; it reappears with dysmenorrhoic symptoms. All disorders become aggravated under the influence of the various noxæ, as perverted physical and psychic life, refrigerations or excessive exertions so frequent at that period of life. The cervix is often the seat of a chronic catarrh. Coitus not infrequently is disturbed by vaginism. Conception takes place either not at all or late; therefore old primiparæ are often examples of infantilism. Pregnancy often terminates in abortion because the corpus uteri with its unequally developed walls cannot adapt itself to the evenly growing ovum. The expulsion of the embryo is protracted on account of the difficult dilatation of the long anteflexed cervix. . . . In the second stage of labor inefficiency of the uterine contractions and in the third stage retention of the placenta with a rapidly contracting os internum are frequent complications. In septic infection the disease assumes the most severe form of puerperal fever."

It is well known that harmonious development and normal growth depend on the inherited constitution, on the normal function of the nerv-

ous system, the presence of the growth-stimulating products of the well balanced, correlated synergistic and antagonistic activities of the complicated endocrin system and on favorable exogenic conditions. General debility and inferiority of the original cell anlage, whereby the cells lack the tendency to multiply and grow normally, deficiency of the growth-stimulating products of inner secretion and untoward external conditions, especially infections, will result in inhibition of development, embraced in infantilism. These evolutionary inhibitions may manifest themselves in manifold morphologic types, complications and degrees, the latter varying from only slight ones to the most pronounced dwarfism (nanism, nanosomia). The chief feature of the clinical pictures is the inhibition of growth, the infantile size and form. Nevertheless dysgenital gigantism (le gigantisme avec infantilisme) has been given its place here, since aside from other infantile characters, to be summarized later, an important function of the progressive childhood stage, namely longitudinal growth, persists in this condition even up to the thirties.

The influence the hormon organs exercise upon the development is selective and partial, that is, each individual gland has a more or less specific sphere of influence, and its deficiency will cause a partial developmental disturbance and inhibition of growth. Although the complicated, mutually interlocked functions of the ductless glands may render it very difficult to circumscribe sharply the pathogenetic position of an individual gland within the often complex clinical picture, a pathogenetic differentiation will be possible in a number of cases since the primarily affected apparatus reveals itself by setting up predominant specific syndromes of its deranged functions. These manifestations lend a more or less characteristic ensemble to the general clinical picture, as seen in the instances of hypofunction of the thyroid, the gonads or the hypophysis.

It was the study of the endocrin system that gave a great impetus to the investigations of the various forms and causes of retarded or arrested development. The importance of the integrity and harmonious solidarity of the hormonopoietic structures is greater indeed in the economy of the growing organism than in mature life, physically and psychically; their disturbances have deeper consequences and are often of somewhat different type. Thus we can appreciate the severity of the detrimental effects upon the young of affections of the thyroid, of aplasia or hypoplasia of the genitals and of certain anomalies of the thymus and pineal glands.

We owe important contributions on infantilism to Anton, Sante de Sanctis, di Gaspero, Falta, Peritz, Tandler and a number of gynecologists, as Hegar, W. A. Freund, Halban, v. Rosthorn and others who have conducted investigations in connection with the various hypoplasias and the asthenic constitution of the female sex particularly.

A number of competent observers as Anton, Peritz and some French distinguish two principal types of general infantilism, namely one of

true endocrino-glandular origin and the other of dystrophic nature. Falta, Mathes, Bauer and others restrict the term to the dystrophic forms, recognizing transitional or combination forms, but ruling out entirely the primary ductless glandular diseases. Whether the first or the latter conception will finally prevail, I consider it justifiable to include both in my discussion for historical reasons and for the purpose of demonstrating the points of issue and the ramifications of the subject; this plan also regards the didactic advantages accruing from a broader comprehension of the subject.

Types of Infantilism

Classification.—The following table of the various types, which is a modification of that of Anton, may serve as basis for ready orientation.

Universal Forms of Infantilism.

1. **Infantilism due to true ductless glandular diseases:**
   - a. *With myxedema and cretinism (thyreogenic).*
   - b. *With absence or underdevelopment of the genitals (dysgenitalism).*
   - c. *With disturbances of the hypophysis.*
   - d. *With disturbances of other glandular structures, as thymus, parathyroids, suprarenals, pancreas.*
   - e. *Pluriglandular infantilism.*

2. **Dystrophic infantilism with the following varieties:**
   - a. *Infantilism in status thymicolymphaticus.*
   - b. *Infantilism with angioplasia.*
   - c. *Infantilism with valvular lesions, congenital or early acquired.*
   - d. *Infantilism due to intoxications and infections of the parents; such as chronic alcoholism, saturnism, mercurialism, morphinism, pellagra, malaria, tuberculosis, leprosy and other endemics.*
   - e. *Infantilism in congenital lues and extra-uterine, early acquired diseases of the offspring, such as tuberculosis, typhoid, severe chronic intestinal insufficiency, interstitial nephritis, liver cirrhosis, etc.*
   - f. *Infantilism in brain diseases; trauma.*
   - g. *Infantilism due to degeneration in unhygienic conditions and due to deficient nutrition of the child.*
   - h. *Infantilism without detectable cause; primary defectiveness of the germinal cell; heredity.*

Gilford divides infantilism into: (A) The essential group, which includes the asexual and sexual types of ateleiosis and progeria; the causes are entirely unknown and the affection is apparently a freak of development. (B) The symptomatic group, that includes all the remainder; the infantilism being secondary to some previous morbid condition.

Fig. 1. Hypothyreogenic infantilism—Brissaud's type. Girl 12 years and 4 months old. Height 43½ inches (normal 58½); weight 53 lbs. (normal 88 lbs.). Head large, face round, somewhat puffy, with cretinoid "worried" expression. Swellings of the subcutaneous tissue above clavicles, over pectoralis muscles, in the lower part of the abdomen and on mons veneris. Skin cool, dry, marbled. Temperament sluggish, intelligence defective. Illustration from author's article on Infantilism. Am. J. M. Sc., 1914, CXLVIII, 251.

The demonstration of infantile conditions of the various organs or organ systems has been much facilitated by radiography, sometimes to a degree impossible by mere clinical methods of examination. Thus, for instance, the topographical relations, forms and evolutionary stages of the thorax, the pelvis and other segments of the skeleton, the stages of ossification, the circulatory organs, the gastro-intestinal tract can be studied with great advantages in their projections on the *x*-ray plate.

As the symptomatology of the various endocrin affections that lead to infantilistic features has been covered in an excellent and exhaustive manner, only summarizing paragraphs with a special bearing on our subject are here justified.

Discussion of Various Types of Infantilism

Myxinfantilism.—This type is most marked in connection with the occurrence of myxedema and cretinism. Hertoghe pointed out that between the "myxedeme franc" (athyreosis) and the functional integrity of the thyroid gland there exist various degrees of deficiency, some of which may be compatible with the intellectual requirements of ordinary life. To these mild forms he applied the term "hypothyroidie benigne chronique," of myxedeme fruste. We meet here all gradations from the distinctly cretinoid habitus to slight, hardly recognizable disturbances which may be ascertained especially through the rapid improvement upon opotherapy.

The individuals appear of diminished size, of a more or less infantile exterior with the proportions and the habitus of the infant in his first months of life; viz., a relatively large head, round "full-moon" face, more or less saddle-shaped nose, a short "lower length," rather cylindrical

trunk, prominent abdomen, low umbilicus and rudimentary genitals. The latter are a manifestation of secondary dysgenitalism with its further consequences, the underdevelopment of the secondary sexual characters. The subcutaneous tissue is not firm but flabby and doughy, though at first sight resembling that of an infant. The skin is not smooth and moist but scaly, rough and dry, the perspiration being absent or very scanty. Radiograms demonstrate delayed ossification. The pulse rate and metabolism are retarded. The face is expressionless but less stolid than in athyreosis.

Fig. 2. Same case as Fig. 1; after 3 years' treatment with thyroid. Pronounced acceleration of growth; entire somatic and psychic change. Original illustration *ibidem*.

The intelligence seemingly is always affected though occasionally only to a slight extent. The perceptive and thinking processes are dull, heavy, slow and clumsy, as seen in the inefficiency or mediocre progress in school. However, the patients may learn reading, writing, and arithmetic, and may pass through the elementary schools even with fair results in exceptional cases. Even where there are present less conspicuous degrees of impairment of the intellect, in the affective sphere the anomaly may be more pronounced, as the monotony of the facial expression demonstrates. The muscular actions are slow, sluggish and clumsy; this is illustrated in their gait. Thus, we notice, some of the characteristics enumerated have rather the stamp of a pathological nature in opposition to the features of the normal infant and the functions of its organs. The various discrepancies, on the whole, convey the impression of premature senility, so conspicuous in the "old age" face of young cretins rather than that of infancy.

Dysgenital Infantilism.—As discussed at length in the chapter on the gonads and their diseases, the sexual glands are not, as are the thyroid, hypophysis or some other ductless glands, indispensable for the existence of the individual; but they exert an important influence upon the organism, especially at the puberty, though to a certain degree also before that period.

Castration in earliest youth causes, as the principal sequelæ, deficiency of the external genitalia and the accessory sex structures, with impotency and absence or underdevelopment of the secondary sexual characteristics,

namely non-growth of the hair about the genitalia, in the axillæ, in the male absence of beard, the hairs on the trunk and the extremities; the persistence of a high pitched voice and the lack of the normal transformation of the psyche at puberty. Due to the lack of the inhibitory or growth-restraining forces that issue from the normally functionating gonads at the end of puberty, the skeletal dimensions, especially those of the extremities, attain an increased length, thus leading to gigantism with a comparatively large span and particularly a preponderance of the "lower length" over the "upper length" of the body. The persistence of the epiphysial discs renders the longitudinal growth possible beyond the normal time, occasionally beyond the age of thirty years. Similar conditions exist among eunuchoids. Tandler and Grosz have offered a splendid presentation of the symptom complex of agenitalism and hypogenitalism, derived especially from their observations on the Skopzes of Russia, in whom castration from religious motives upon a large scale offered opportunity to study its effects. These observers distinguish two clinical forms of dysgenitalism, namely gigantism and dysgenital obesity, with transitional forms. They have been discussed in other chapters.

Fig. 3. Infantilism of Brissaud's type. Patient seven years old; beside a normally developed boy of the same age. Her weight 20 lbs. (normal for the age, 49 lbs.), her height 29 inches (normal for the age 45 inches); expressed relatively, this child at seven years has a weight normal to one of ten months, and a height to one of twenty months. Original illustration in Griffith's (J. P. C.) article on Infantilism. Am. J. D. Ch. 1918, XVI, 105 (Fig. 1).

There is no doubt that a number of the somatic characteristics correspond to those of childhood, so that such competent authors as Anton, Peritz and several among the French felt induced to classify eunuchoidism as a dysgenital form of universal infantilism (Gigantisme avec infantilisme). But other investigators as Falta, Tandler and Grosz do not accept this classification and, as mentioned before, restrict the term infantilism to those forms that have infantile or childish dimensions, to the so-called dystrophic types of our classification.

Eunuchoids, indeed, if complications are absent, are, on the contrary,

at least not reduced in size, and the proportions of the skeleton are wholly different from those in children. The complexion of the face in the young eunuchoid is delicate and pale, but soon turns sallow, wrinkled and senile (Geroderma genito-dystrophico).

However, Peritz, in a recent publication on this subject, again insists with emphasis upon the numerous features that dysgenitalism has in common with the immature state of childhood, justifying its place among the forms of universal infantilism. Such features are deficiency of the genitals, absence of the secondary sexual characters, persistence of the epiphysial junctures, infantile pelvis, infantile cartilaginous larynx with a high-pitched voice, abnormal development of the fat tissue, not unlike the adiposity of children during their stage of "fullness"; progressive growth of all parts of the body, persistence of the thymus and psychic infantilism.

The abnormal growth is not due so much to hyperfunction of the growth-stimulating organs as to lack of the antagonistic hormons that exercise a restrictive influence on growth, the products of normally functionating gonads at puberty.

Not infrequently at the time of rapid growth during puberty a temporary lagging behind of the gonads in their development and function leads to a transitory though perhaps well marked syndrome of eunuchoid adiposity that later disappears with the rallying of the endocrin secretion (Prepubertial eunuchoidism). Such a forme fruste is exemplified by Falta's observation (No. 48, page 398), concerning a 13-year-old boy.

Nanosomia of Hypophysial Origin

Hypophysial Infantilism.—Due to the paramount position the hypophysis holds in the chain of the hormonopoietic system as one of the controlling factors of growth and due to its relation to other endocrin glands, especially the genitals, marked developmental anomalies will result from its derangement, whether the latter are caused by a primary disturbance of that organ, such as hypoplasia, tumor or sclerosis, or by other endocranial conditions in the vinicity or more remote, that directly or indirectly interfere with its function, such as tumors or hydrocephalus.

From clinical observation and experimental pathology we know that hypophysial dystrophy, which begins in the young, is followed in most cases by a retardation or cessation of the growth of the skeleton and ossification. The size of the body remains below the average and is occasionally decreased to the diminutive measures of veritable dwarfism with a length of only from 56 to 54 inches or less. The external sexual organs remain in an immature state, though occasionally penis and testicles may be normal and functionate well. The perigenital hairs are usually absent or scanty, and in the male have boundaries of the feminine type; the

Fig. 4. Hypophysial adiposity. At the age of eight years following typhoid fever striking adiposity began to develop; for six years headache daily. Patient 21 years old. Height, 57⅞ inches, the size of a normal thirteen-year-old boy; weight 133 lbs. Head large, face round with immature expression. No beard or mustache. High pitched voice, small, graceful, feminine hands. Eunuchoid localizations of adipose tissue. Penis small, deeply buried under the cushion of adipose tissue of the mons veneris. No libido sexualis; rarely erections. Epiphysial discs of the phalanges and metacarpals not yet ossified. Author's case fully described in his article on Infantilism. Am. J. M. Sc., 1914, CXLVIII. Original illustration, p. 256.

voice is high-pitched, the beard absent; in short, the secondary sexual characteristics are not normal. The face is round, fat, its expression very childish, soft, without manly strength and character. A prominent feature is endogenous adiposity, conspicuous by its "eunuchoid" localizations more than by its degree. Deposits of fat tissue are especially noticeable in the mammary region, on the hips, and nates, on the thighs, as in women, or small, well-fed children; in the lower half of the abdomen that, as in infants, is separated by a deep furrow from the excessive fat pad on the mons veneris. The hands and feet have likewise an infantile character, in that they are small, graceful, chubby, and dimpled, and reveal a retarded ossification in the röntgenogram. Interesting and bearing on the extent of similarity between hypophysial dwarf and child are the results derived from a more accurate comparison of the proportions and topographic relations of certain parts of the head of hypophysial dwarfs with the corresponding data in the normal child and adult. Mayer and Peritz in their articles on infantilism illustrate these anatomical relations by a number of drawings.

According to the canon of the anthropologists the face proper is the part reaching from the lower edge of the chin to the eyebrows; the part above is the skull. In the adult the eyebrows are situated above the middle of the total height of the head, the proportion of the height of the face to that of the skull being 4 to 3; whereas in the child the eyebrows are located in the middle of the height of the head, the skull being relatively larger than in the adult and rather of globe shape. Until the sixth year of life the face (in the anthropologic sense) is broader than long, its length being somewhat smaller than the distance of the external canthi of the eyes. This form represents an inferior stage of development (Mayer). During the stage of growth the oblong form of the face of the adult develops as the result of the only comparatively slight increase of the distance of the external canthi. In hypophysial darfism, as Peritz demonstrates by an illustration, the head occupies an

intermediary position by its proportions and shape; its configuration retaining some infantile characters. In addition to that, the total height of the head in comparison to the body is greater than in the adult, thus approaching the infantile proportions also in this respect, and enhancing the impression of immaturity which the general aspect gives. Paradigms of nanism of this group were reported by Paltauf (112 cm.), Hueters (106 cm.), Burnier (125 cm.) (cited by Peritz), Falta, Priesel and others.

Many varieties deviating from this classical type do occur, without completely obliterating the original, depending on the age of the patient at the beginning of the affection, the degree to which the anterior and the posterior lobe of the hypophysis or the base of the midbrain with its center of metabolism is involved and according to the degree of secondary dysgenitalism. Where manifest cachexia would be associated with hypopituitarism (as in the observation No. 45 of Falta) the clinical differential diagnosis from multiple ductless glandular disease would be difficult.

Fig. 5. Frontal view of Figure 4.

A brief discussion of those not infrequent cases of monstrous adiposity of pituitary origin may be permitted, which Neurath (*a*), under the title "Fettkinder," has described and illustrated. A characteristic instance was the following: A boy, aged ten years, developed a monstrous adiposity at seven years of age following scarlatina; the growth was remarkedly retarded, and the boy suffered from attacks of headache and vertigo. His height, 109 cm., corresponded to that of a normal boy of six years, while his weight, 36.8 kgm., was that of a 13-year-old boy. The circumference of the head was 53 cm. The testicles were well developed; the penis was hidden in the adipose tissue of the mons veneris. The radioscopic examination of the skull revealed signs of hydrocephalus, but a normal sella turcica. Neurath asserts that an affection of the hypophysial gland in this and similar instances may be caused by a hydrocephalic effusion due either to serous meningitis complicating scarlatina or to a small tumor, escaping the detection by the *x*-rays.

In analogous cases, as those reported by Marinesco and Goldstein, Babonniex and Paisseau, Kruckemann, and Kurt Goldstein, the pathogenetic factor was a pressure lesion with consequent functional deficiency of the hypophysis through hydrocephalic effusion that distended the third ventricle. Among the patients some are of strikingly small size and have

large heads. In one of the cases of Babonneix and Paisseau adiposity started after scarlatina, as in the patient of Neurath, and in one of my own observations after typhoid, complicated possibly by serous meningitis, with chronic hydrocephalus resulting. Cushing in his elaborate monograph on the pituitary body expresses the view that secondary changes

Fig. 6. Extreme obesity in a boy 2 years, 9 months old. From the beginning of the second year of age a rapid gain in weight took place. Body weight 24.82 kgm. (54 lbs., 9.5 oz.); height 94 cm. (36⅞ inches); mental deficiency. After administration of pituitary extract the boy lost weight and commenced to develop mentally. From Talbot's article Am. J. Dis. Child., 1920, XX. Original illustration Fig. 1, page 332.

probably occur in the hypophysis in every case of increased intracranial tension, often with gross deformity and resultant functional disturbances which frequently elicit recognizable manifestations. He reviews the then scanty literature on the relation of hydrocephalus to the pituitary gland.

From the various reports it appears that the type of adiposity under

discussion may occur with or without clinically visible disturbance of the genital organs (dysgenitalism). Biedel in 32 cases of hypophysial adi-

Fig. 7. Rear view of same patient. (*Ibidem*, page 334.)

posity found only 12 with genital atrophy. An extreme case of obesity in a child has lately been illustrated by Talbot.

Multiglandular Infantilism

Due to the interdependence of the individual glands of the endocrin cycle primary anatomical lesions of one member will also cause others to suffer to a certain degree. In myxedema, for instance, athyreosis is admittedly the principal but not the exclusive pathogenetic factor, inasmuch as the chromaphil tissue, and especially the germinative glands, are more or less involved. In fact, according to Sante de Sanctis, the whole hormonopoietic apparatus participates. In hypopituitarism we find dysgenitalism particularly. These disturbances, however, are secondary and only functional, and with the restoration of the primarily affected

organ or with the disappearance of the myxedema under specific organotherapy the gonads and suprarenals resume approximately their normal function. In atypical cases of spontaneous myxedema, Addison's disease, or late eunuchoidism, however, the anatomico-pathological process itself may, to a certain degree, involve also other glands. These forms present transitions to those of pluriglandular disease in which a serious primary anatomical process, namely hypoplasia, or inflammatory sclerosis and atrophy affect several or all glands more or less simultaneously; the thyroid, genitals, hypophysis and suprarenals especially participate, though other structures also may be involved, as the parathyroids, the pancreas, liver and kidneys.

The complex clinical picture to which Claude and Gougero in their fundamental essay on "insuffisance pluriglandulaire endocrinienne" have directed our attention, is therefore characterized principally by the combination of signs of hypothyreosis, hypophysial deficiency, eunuchoidism and morbus Addisoni with progressive cachexia, as exemplified by the instructive case of the two authors and by a number of observations of others. The progressive cachexia, for which the sclerosis of the pituitary body is partly responsible, probably prevents the otherwise expected hypophysial adiposity in the clinical picture.

As the associations of pluriglandular insufficiency are numerous and of different degrees, it is evident that there exist a series of syndromes that vary according to the glands affected, the degree and succession of the disorder of each individual ductless gland, and the age of the person. While in the adult retrogressive symptoms develop as discussed in another chapter, in the young and congenital cases, multiglandular derangement must needs result in formal infantilism with retardation or cessation of growth, as the growth controlling organs are involved. The formation of eunuchoid long-leggedness as due to the effect upon the skeletal development of the failure of gonad function, however, may be entirely counteracted by the simultaneous hypophysial inactivity. Pluriglandular sclerosis has been observed associated with or resulting from tuberculosis, lues, possibly alcoholism or following acute infectious diseases; it may also appear spontaneously as a seemingly independent disease of rather obscure origin. Claude and Gougero assume a congenital debility of the endocrin system for such cases, liable to degeneration under the influence of a not well definable noxa.

That pluriglandular insufficiency during the growing stage may be of only transitory nature is evident from the observation (No. 54) of Falta. The patient, J. K., 17 years old. He had typical tetany and epileptic attacks; was of medium size; the skin was dry and the face and hands myxedematous. Hairs of the beard, in the axilla, linea alba and on calves were absent; there was scanty hair at the root of the penis. The testicles were very small; he had no libido, erections or pollutions. The finger

nails were strongly curved and ridged longitudinally, and the teeth poorly developed. Blood pressure was 65. The administration of 200 grams of dextrose caused no glycosuria. He showed slight apathy. Upon thyroid therapy disappearance of the myxedema and rise of blood pressure to normal occurred. A year later he still suffered from tetany, but no myxedematoid symptoms. The secondary sexual characters for the greater part had developed and the sexual life begun to assert itself. Thus, in addition to typical tetany and epilepsy there existed signs of disturbance of the thyroid, the genitals and perhaps the suprarenals (marked hypotonia).

Instances of pluriglandular syndromes with infantilistic features were described by Richon and Jeandelize, by Peritz, Campioni, Nazari, Pende and others. In the case of Nazari there were present infantilism, tuberculosis of the lungs and meninges, cystic degeneration of the hypophysis, persistence of the thymus gland, hypoplasia of the testicles and the thyroid. The patient of Morlat also had, according to the interpretation of Claude and Gougero, signs of lack of function of the thyroid, the adrenals and testicles. Thompson described a noteworthy case of sclerosis in all ductless glands occurring in primary infantile atrophy, so that the possibility of the existence of a multiple ductless glandular affection may be considered in a number of instances of pedatrophy.

Dystrophic Infantilism

This form was first described in 1871 by Lorain, after whom it is generally named. It differs morphologically and etiologically from the type of Brissaud. The affected individuals are small, but graceful; they have "elegant, fine" forms; the extremities are long, the abdomen is not prominent, the adipose tissue not increased, and the contours of musculature and skeleton are therefore not masked. This is in contradistinction to Brissaud's hypothyreogenic type. Though the genitals are diminutive, they are about proportionate to the body size. The intelligence is mediocre —childish like the body. The type resembles "un homme miniature," and presents, as Meige tersely says, the picture of a normal individual seen through an opera glass reversed.

As already mentioned, Falta, with others, restricts the term infantilism to this form and defines it as an arrest at the infantile stage of development, hence presenting the following principal characteristics: deficient growth; retarded ossification, namely delayed appearance of the bone nuclei and late closure of the epiphysial junctures; retention of childish dimensions of the body, either wholly or in part. That is, the "lower length" of the body equals the "upper length," or more commonly, slightly exceeds it. The form of the pelvis is neither masculine nor feminine

but infantile. The involution of the lymphatic apparatus is deficient, the genitalia, secondary sexual characteristics and vita sexualis are deficient or undeveloped. The psyche also remains infantile.

Fig. 8. Lorain's type of Infantilism. Boy twelve years, four months old. Height 50½ inches (normal for this age 55.4 inches). Weight 42 lbs. (normal 76.9 lbs.) Graceful stature, delicate skeleton. Testicles small, penis 1¼ inch long. Crines pubis scanty. Psychic deficiency. At present (20 years old) his height is 4 feet, 6½ inches, his weight 65 lbs. Author's case, fully described Am. J. M. Sc., l. c., CXLIII. Original illustration Fig. No. 5, page 261.

Infantilistic features naturally become more manifest, apart from extreme cases, the closer the individual approaches that period at which the evolution should be completed. Near or at puberty perhaps, for the first time, infantile organs will reveal their functional failure clearly; this is especially the case with the genital glands.

Von Rosthorn, in a classical description of the infantile habitus (asthenic form) in woman, enumerates the following morphological attributes: Growth is diminished, the skeleton is graceful and with the childish proportions, viz., short lower extremities; the typical curvings of the vertebral column are only slight, the pelvis is hypoplastic, of lessened inclination, and the hips are narrow; the facial skeleton is underdeveloped, for the chin and the jaws are hypoplastic and the nose is infantile; the mastoid processes are small. The musculature is poorly developed. The nates are flat, the growth of hairs is scanty, especially on the underdeveloped mons veneris. The breasts are childish in form with only a little parenchyma and a small areola and the nipples are often flat or retracted as is characteristic of the fetal stage. Typical alterations are evident in the genitalia. The external parts are hardly covered by the flesh of the thighs as in normal woman and the internal parts show typical hypoplasias. The funnel-shaped vulva is suggestive of the original urogenital sinus. With this are associated developmental anomalies of the kidneys, cecum and the lower end of the intestinal tract, not demonstrable clinically. The total picture of the general habitus includes also the infantile heart, the narrowness of the circulatory system and frequently, during puberty, a disturbance of the correlation of those organs that are responsible for the integrity of the blood tissue. Finally also the psyche is infantile.

Etiology and Pathogenesis.—In the etiology of dystrophic infantilism the most divergent deleterious agents which call forth a debility of the whole constitution of the organism come into consideration. This form is encountered sometimes accompanying the status thymicolymphaticus, valvular diseases,

and under certain conditions also as a consequence of long continued infections, especially of lues; in descendants of parents who are suffering from chronic alcoholism, morphinism, saturnism, pellagra, tuberculosis, malaria, leprosy and other endemic diseases; in individuals who live in poor, unhygienic surroundings and suffer from various deprivations, especially from insufficient alimentation. In other cases, in which no definite cause is discoverable, the presumption of a primary defectiveness of the germ plasm or an original deviation from the normal of the Keimanlage, possibly based upon inheritance must be resorted to. Joffroy describes infantilism associated with "paralysie générale juvenile," and Falta observed it in combination with progressive muscular atrophy. But it must be insisted that none of these causes alone will give rise to dystrophic infantilism; probably circumstances not well known in the concrete cases with inborn tendencies must coöperate.

The question as to the rôle played by the ductless glands in dystrophic ("true") infantilism remains still *sub judice*. The tendency is coming more and more to the fore to assume that even where a chronic disease early in life has been followed by dystrophic infantilism, this faulty development is really the effect of the altered relation of one or more endocrin glands or is due to direct changes in the histologic structure and resulting dysfunction of the pituitary body. Hertogh's exclusive viewpoint that the thyroid holds a central position even in the presence of these causes enumerated (lues, etc.), that only a preëxisting disturbance of the thyroid or one provoked by these agencies could bring into existence an infantilistic stunting of growth, is no longer tenable, in the face of accumulating clinical facts. Ferranni and others have pointed out many cogent reasons militating against this extreme contention. In the view of some investigators it is more probable that not one hormone gland is particularly responsible but rather the entire endocrin system participates more or less in the general developmental affection. Falta cannot share the theory that in dystrophic (true) infantilism the endocrin glands hold any important pathogenetic position and argues that during the standstill of the entire organism at the childish stage of development naturally the ductless glands system likewise remains infantile, just as do the skeleton or the nervous system. He considers the hypoevolution of the endocrin chain to be merely coördinate with that of the remainder of the organism. Indeed we see at least no evidences of disturbed correlation among the ductless glands: they functionate harmoniously but only on the scale fully suited to the childish conditions. There is no falling away of the genital function, for signs of eunuchoidism are lacking; but the function is that of childhood, thus explaining the lack of secondary sexual characters. The sexual glands of "true" infantilism or the infantile genitals are essentially different from those of eunuchoidism. Also anomalies of skin, adipose tissue, metabolism, body temperature, etc., peculiar to true

endocrino-glandular diseases are not features of dystrophic infantilism. The latter, therefore, is to be considered rather a harmonious developmental inhibition, a vegetative disturbance of a general nature of the organism in its totality. There may exist combinations of dystrophic infantilism with hypophysial or eunuchoid forms of dystrophia adiposogenitalis, transitional types that pass over into the true primary ductless glandular diseases; combinations with true hypothyroidism, pronounced status lymphaticus, or with other vegetative disturbances, as mongolism, etc. Falta's case (No. 61), a heredoluetic boy, affected with dystrophic infantilism and manifesting a more or less noticeable eunuchoid distribution of fat tissue, represents such a mixed form.

Dystrophic Infantilism in Status Thymicolymphaticus.—The status thymicolymphaticus with its clinical and anatomical varieties is the subject of another chapter in this handbook; therefore only a few remarks will be made here. This constitutional anomaly is not associated with formal infantilism in every instance. Bartels measured thirty individuals and found that ten had exceeded while only five were beneath the average size, the reduction of the body length being not more than 4.9 per cent. In other instances the growth may be much stunted. It is probable that lymphatic hyperplasia and the associated developmental anomalies of other organs, such as the vascular hypoplasia, genital deficiency, faulty evolution of the chromaphil system, etc., are coördinated manifestations of a general congenital hypoplastic constitution that manifests itself in all parts, organs and their functions; that it represents in the true sense a trophic disturbance, from the beginning of the development of the individual (Bartels). Its farther sequelæ are sometimes infantilism or at times chlorotic or angioneurotic symptoms. To what extent the responsibility may be due to a disturbance of the internal secretion of the lymphatic apparatus and its correlation with the central nervous system, and with other endocrin glands, especially the genitals, is not definitely established, and some authors accord to this variety of infantilism an intermediary position between the dystrophic and endocrino-pathologic forms.

Infantilism Due to Heart Lesions.—Infantilism may be the consequence of heart lesions (nanisme cardiaque), either congenital or early acquired and chronic, especially of mitral stenosis (nanisme mitral) or pulmonary stenosis. It is not due to any bacterial toxins but probably to faulty circulation with impaired oxygen supply to all organs and the consequent retardation and impairment of all nutritional processes, especially detrimental to the growing organism. However, one should not overlook that congenital vitium cordis frequently is complicated with other developmental anomalies or malformations that may contribute to create infantilism, as instanced by the observation of Recklinghausen. The patient, a woman 25 years old, affected with infantile habitus, in addition to a small heart with widely

patulous foramen ovale, had also a narrow aorta, lobulated kidneys, long narrow urinary bladder and ovaries, considerable residues of the thymus and infantile genitalia and pelvis. Congenital vitium with narrowness of the aortic system may be not only a cause but also perhaps in many instances a coördinated manifestation of infantilism. That general hypotrophy of the body is by no means a constant complication of vitium cordis, be it congenital or early acquired, is a common observation. Weber, among his numerous cases of vitia cordis in childhood, could trace a general hypotrophy to cardiac anomalies in only eight instances.

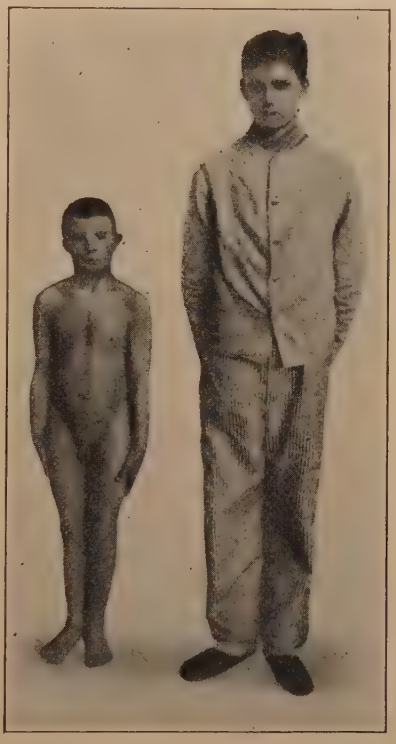


Fig. 9. Sixteen-year-old person with early acquired vitium cordis; beside a normally developed youth of the same age. Original illustration, Fig. No. 13 in Peritz's article on Infantilism; Ergebn. d. inn. Med. u. Kinderh., Berl., 1911, VII, page 460.

Infantilism Resulting from Chronic Intoxications and Infections.—Important factors under certain circumstances leading to defective development of the whole organism are the various intoxications and infections enumerated in a foregoing chapter. The infectious diseases may exert their influence either by devitalizing and debilitating the germinative organs and the germ cells of the progenitors or by affecting the offspring itself during the intra-uterine or postnatal life, so that the growth energy is impaired. In two of my cases of atrophic infantilism the mothers had suffered during gestation from severe febrile rheumatic polyarthritis, a condition that is suggestive as having a bearing upon the general dystrophy of the new-born.

Children suffering from severe tuberculosis of long standing in any part of the body frequently show retarded or arrested development, and spinal caries is comparatively a common cause of this retardation (Infantilisme pottique of Marie et Levi, Debove, Claude et Lejonne). Typhoid in early youth caused infantilism in the case of Apert and Rouillard.

The relation of malarial infection to dystrophic infantilism is evident from the comparative frequency of the latter in malarial districts. Ferranni in Cicily and H. de Brun point to the numerous emaciated, dystrophic subjects of small figures and senile countenances among those who have suffered from malaria in early life. I saw similar conditions

in some parts of Syria in 1900. Differing morphologically from the slender "graceful" forms of Lorain's type these persons have enormous abdomens due to the intumescence of the spleen and liver. Grotesque figures result from this contrast of general emaciation and enlarged abdomens. Orgeas calls attention to the stunting effect of parental malaria upon the offspring of Europeans in French Guiana. He emphasizes the extreme smallness of the body, the flabby skin, the atrophy of the male genitals, and microcephaly as main features of these "variations morbides." This degeneracy of the children, especially of the males, from chronic malaria and deterioration of the parents, is one of the chief causes of the extinction of the unmixed white race in the tropical (malarial) lands.

General Syphilidotoxic Dystrophies.—The damage inflicted on the organism by congenital lues not infrequently assumes a character far beyond the importance of a mere local affection, by involving the organism in universal dystrophy as the remote effect of a local organ lesion, specially of alterations of one or several of the members of the endocrin cycle with subsequent dysfunction. Thus thyreogenic syndromes in early childhood or in adolescence, hypophysiary dystrophies, nanism, acromegaly even in the young, including formes frustes of it, dystrophia adiposogenitalis, gigantism and clinical pictures dependent upon disturbances of the suprarenals and finally pluriglandular symptom complexes have been described. Hutinel in his recent publication on hereditary lues and its dystrophies enlarges on this subject in a masterly manner, illustrating it with numerous personal observations of the various types.

Pentagna among twenty thousand children found 115 with dysfunction of the endocrin system, namely myxedema, hypofunction of the suprarenal apparatus, pluriglandular disturbances and Mongolian idiocy with congenital lues assured in 46 per cent. In only 23.4 per cent could hereditary lues be excluded and other etiologic factors held responsible, such as chronic alcoholism, hereditary endocrin affections, disturbed pregnancy, etc. This high percentage seems to indicate the great influence of the luetic infection upon the development of endocrin dysfunction.

But another group of general dystrophies not infrequently assumes the clinical aspect of Lorain's type of degenerative infantilism. It is not surprising that inadequacy or especially lack of specific treatment should have a bearing upon the establishment of the latter. While in the experience of some authors such as Hochsinger, luetic infantilism occurred only in children that had marked heredoluetic manifestations during the first weeks of life. Peritz and others observed it especially in those in whom previous severe local manifestations were absent. These writers point to the striking analogy with tabes dorsalis, which if occurring as the juvenile form is often combined with infantile habitus. The general dystrophy may at first, perhaps, be only to a slight extent manifest,

but at puberty becomes more evident, especially in the retardation of the sexual apparatus. Hochsinger considers the possibility of general vascular alterations playing hereby a rôle, since such were found in all his cases.

Intestinal and Pancreatic Infantilism.—Dystrophic infantilism has been occasionally observed in connection with chronic disorders of the gastro-intestinal tract with consequent malnutrition and atrophy. However, we must not lose sight of the fact that infantilistic constitution from any cause may predispose to intestinal insufficiency as to other diseases, such as tuberculosis, etc., forming thus a vicious circle. Babies with poor digestion and assimilation are puny and meager for a long period of time and their psychic progress is also retarded. This delay in most instances is only temporary. However exceptionally the individuals affected may remain small, puny, dystrophic in the full sense of the term. The principal factor is a very severe chronic intestinal insufficiency with much reduced function of the digestive glands which is rather refractory to treatment and as a rule affecting children beyond the stage of infancy. The tolerance for fats and carbohydrates is reduced so that slight dietary indiscretion or a minor parenteral infection brings on a digestive disturbance of severe nature with marked loss of body weight and a reparability of function far below normal. But also without such recognizable causes obstinately relapsing diarrhea of a fermentative character will occur. In addition, or rather as a consequence of this, the somatic development becomes seriously impaired and finally the children are set back in body weight and height by years. The clinical syndrome has led Herter to speak of intestinal infantilism. In 1909 he described several children, all underdeveloped due to chronic relapsing diarrhea. The feces had a characteristic bacterial flora (Bacillus bifidus, Bacillus infantilis), were voluminous, gray or light brown in color, usually gruel-like in consistency and of sour odor and excessively fatty. There existed a moderate degree of anemia, flabbiness of the musculature and marked meteorism.

Similar clinical observations are communicated by Freeman, Heubner, Schulz, Moorhead and others and undoubtedly have been made by many of us. As this form of infantilism does not originate from a primary deviation of the Keimanlage from the normal or some anatomical lesions, but is due to a functional insufficiency, the prognosis is not gloomy in spite of the most severe atrophy these children present. The great majority of the cases under proper treatment finally gradually recover (Heubner). H. Gilford classifies this type as infantilism by deprivation.

Byrom Bramwell (*a*) in 1904 described what he termed pancreatic infantilism, which undoubtedly is allied to the foregoing type. His patient was a male, 18½ years old, with the aspect of an eleven-year-old boy. From his ninth year he had diarrhea. The epiphysial cartilages were still ununited. Under treatment with pancreas for two years the patient grew 5⅞ inches in height and gained 23¾ pounds. The sexual develop-

ment became normal. The same author in 1915 reported an additional number of cases of cessation of growth, sexual infantilism with good psychic progress, caused by chronic diarrhea in connection with pancreatic insufficiency. Administration of pancreas extract corrected not only the diarrhea but strikingly improved the entire physical development. Quite similar observations are recorded by Rentoul and Moorhead. However, the question arises whether the infantilistic syndrome is directly due to a disturbance of the exocrin and endocrin secretion of the pancreas or to the constant diarrhea, and the ensuing nutritional impairment, so that as a result of the cure of the diarrhea by opotherapy an improvement of the general development takes place.

Fig. 10. Infantilism due to severe chronic intestinal insufficiency. Boy seven years old, beside a normally developed boy of the same age. Since his sixth month of life very frequent attacks of severe diarrhea lasting 1½ to 2 weeks. Stools voluminous, three to five daily, liquid, malodorous. Meteorism. Body weight, 25 lbs. Height, 33½ inches. (Cook County Hospital case No. 762606.)

To R. Miller it appears that the types of infantilism spoken of as pancreatic or intestinal are all the same condition, namely such as result from celiac disease; he uses the term celiac infantilism, which term is noncommittal as to the cause of celiac disease, while clearly denoting a type of infantilism in which the impairment of development is due to that malady. Its three cardinal features are enlargement of abdomen, persistent or relapsing diarrhea with pale fatty stools and retardation of physical growth and development.

That diabetes mellitus, the prototype of endocrin pancreatic disorder does not lead to infantilism notwithstanding the oftentimes severe emaciation and other phenomena of a deeply disturbed metabolism, may find its explanation in the usually very rapid course of the disease that "in childhood grants no pardon" (von Noorden) and issues in exitus lethalis.

Bullrich, however, reported a case similar in the clinical aspect to those of Bramwell, but with the difference that there was present also diabetes mellitus. The patient at the age of nine years was normally developed. At 11½ years emaciation, polyuria, polydipsia and constipation set in. Later there was continued severe diarrhea with steatorrhea. The body weight at 16 years of age was only 21 kilos. The sexual organs were not developed; suprapubic and axillary hairs were absent, the hair on the scalp was scanty, the face senile, the skin wrinkled. There was deficiency of the exocrin and

endocrin secretion of the pancreas with diabetes. Pancreas extract was administered without any result. The autopsy revealed, in addition to changes in the pancreas, a pronounced hypophysial and thyroid affection and hepatic cirrhosis, justifying, in the opinion of the writer, the classification of the case among the pluriglandular diseases.

Amenta described pancreatic diabetes with "pancreatic infantilism" in a boy 8 years old weighing 7400 grams who from the end of the first year had suffered from pancreatic diabetes.

M. Landoli reported a case of infantilism of gastric origin. The patient, aged 20 years, was the size of a ten-year-old boy; the stunted growth was caused by gastrosuccorrhea of long duration.

Varieties of Dystrophic Infantilism in Hepatic and Renal Diseases.—Finlayson reports the case of a twenty-three-year-old man who suffered from biliary cirrhosis. His weight was only 35½ kilos. His brother, aged nineteen years, likewise suffered from this hepatic affection and had a weight of 31 kilos. Hasenclever published three cases of infantilism in one family associated with liver cirrhosis; and similar observations are reported by Hutinel, Taylor, Gilbert and Fournier, Lereboullet, Cautley, Falta (observation No. 60).

Otto May speaks of renal infantilism in congenital or early acquired chronic interstitial nephritis and in connection with diabetes insipidus. Observations pertaining to this category of infantilism have been contributed by Miller and Parson, Fletcher, Naish, Miller, Sutherland, Weber, Cherry, Porter, Holt and others. That infantilism associated with diabetes insipidus may be of hypophysial origin appears certain in the light of our knowledge of the relation that exists between the pituitary body and polyuria. (Case of Antonelli.)

Infantilism Resulting from Brain Lesions; Traumas.—Lesions of the brain, as encephalitis or microcephaly, porencephaly and other developmental cerebral abnormalities, embraced in the clinical group of cerebral infantile paralysis, and also progressive paralysis in early life may project themselves somatically in a defective general development with reduced longitudinal growth and body weight through the interference with the normal influence of the central nervous system upon the bones, musculature and the various glands and organs. Indeed a striking parallelism exists in idiots between the weight of the brain and that of the organs and between the weight of the brain and the duration of life, as established by H. Vogt's investigations. The reduction in size of microcephalic individuals may bring the body within the compass of the small brain, so that the smallness of the skull would not in itself attract our attention. In many idiots also the function of ossification was found to be irregular. Interesting data on the growth in length and volume of idiotic children are contributed by Dollinger in his recent publication on Idiocy.

In the experience of Anton, traumas also, and especially those due to

violent general concussion, may be of great pathological importance in causing young individuals to remain in the stage of development which they had attained at the time of the trauma. Stunted growth had followed concussion of the brain in a seven-year-old child, observed by Falta (case No. 56).

Infantilism Due to Unhygienic Surroundings and Malnutrition.—Depressing circumstances of life, improper feeding, irregularity and lack of sleep, crowded conditions in ill-ventilated and lightless rooms and other obnoxious factors and evil influences summarized under the term "unhygienic surroundings" often, through their combined effect, give rise to poor physique. This is a matter of common observation in the slums of many large cities. H. Gilford demonstrated the existence of what is tantamount to endemic infantilism in the slum districts of London. The individuals affected are warped both in body and mind, live short lives, readily succumb to disease and break down at an unusually early age with senile decay. Peritz found an enormous percentage of physical and psychic infantilism in the Rumelsburg orphan asylum, occupied by the children of the lowest social strata of Berlin. The inmates are physically and mentally three years behind those of the same age who live under favorable conditions. The disparity increases with age so that youths 15 to 16 years old have the appearance of those of ten to twelve years.

On a scale unparalleled, because of the involvement of entire nations of previously vigorous physique, the direct stunting effect of qualitative and quantitative chronic underfeeding and starvation is encompassed by the common experience in the recently war-ridden countries of Europe. Yet an astounding recuperative faculty of the growing organism is to be observed, when placed under improved food conditions.

Progerio as a Manifestation of Infantilism.—Very uncommon disease pictures of an exceedingly pronounced type were described by Hutchinson, Gilford (*a*) (*e*), Variot and Pironneau. They have been designated by Gilford "progeria," and by Variot and Pironneau "nanisme type senile." Since the three cases clinically are in every essential very similar, all striking by a senile appearance of high degree and enormous cachexia, as seen also from their photographic illustrations, only the case of Gilford is here briefly abstracted.

The boy, 15 years old, had a very small childish stature; height 113 cm., weight 16 kilos. There existed extreme leanness, so that the bones, tendons and veins were revealed with striking clearness. The general aspect was that of a very pronounced senility; the skin was very thin, dry, old-looking. Save for a sparse growth of fine gray hair on his scalp, eyebrows and eyelids, he was destitute of hair. There were still many deciduous teeth remaining; the anterior fontanel was not yet closed, the voice was piping (falsetto). The genitals were similar to those of a normal subject a year or two younger. Exitus lethalis occurred at the age of

eighteen. The necropsy revealed in the internal structure a curious mixture of youth and old age. There were extensive atheroma of the heart valves and coronary arteries; an enlarged fibrous thymus gland; fibrous, senile kidneys and shriveled suprarenal capsules. The stomach and intestines were so atrophic as to be almost transparent, resembling wet paper. The ossification was a little premature. Gilford concluded that progeria is a premature senile decay affecting the body as a whole, arising in an individual in a state of infantilism and manifesting itself as is usual with senility in some organs more than in others.

Psychic Infantilism.—The psychic sphere participates in various degrees also in the developmental retardation or arrest in the different forms of universal infantilism. Although a juvenile aspect in the adult may be associated with psychic and intellectual maturity, perhaps most often it is mingled with psychopathic features. On the other hand, psychic infantilism occurs not infrequently isolated in individuals somatically *well developed*. This is a partial infantilism, representing a disturbance limited to the psychic organ. De Sanctis in his fundamental publication places the inhibition of intelligence and character development side by side as equally important with the main symptoms of somatic infantilism, namely, the arrested growth of the body and the infantile type of the genitals. Since infantilism is an arrest of growth in the stage of childhood, it is evident that the subjects may at first demonstrate no signs of deficient psychic evolution, but that later, especially at puberty or thereafter, the inadequacy of the psychic progress, the disparity between real age and the psychic age will become manifest more and more. Anton instances two women in whom too early gravidity was responsible for the psychic arrest at the juvenile stage. Frustrated forms are not uncommon, and grade off to the normal.

Psycho-infantilistic features may appear as a partial manifestation in certain neuroses, as in hysteria. Janet, in concluding his able exposé, spoke the words that have been much quoted since: "Who has not repeatedly exclaimed at the examination of a hysteric, 'again a child.'" Certain psychic stigmata of immaturity are met with not infrequently also in adult ticqueurs. For the awkwardness and lack of voluntary control of movements Meige coined the term infantilisme moteur. Psycho-infantilistic features are seen also in the disequilibrated and in the subjects of "nervousness of the only child" (Peritz), characterized by lack of self-control, unstability, capriciousness, unbridled affects, egoism and effeminacy, as the result of faulty family influences. The principal features of psycho-infantilism are lack of self-reliance, a great need of counsel and advice by others, an attention easily attracted but very fugitive, a childish carelessness, cheerful, very changeable, fickle mood that to a great extent mimics the disposition of others; the timidity and egoism of the child. There is also a lack of the faculty to differentiate the essential

and important from matters of secondary import; the judgment remains superficial and is like the irresolute will readily influenced and swayed by suggestion. There is a strong inclination towards superstition, a naïve conception of life and lack of logic. Though overduly impressed by strangers, on the other hand the subjects are often prejudiced, stubborn and inaccessible to the advice of relatives. The memory may be impaired by direct defects or unreliable on account of erroneous additions, exaggerations, embellishments of experiences, a pleasure in fabricating adventurous stories and a great indulgence in fairy tales. As among the degenerates also here do we observe inferior and superior types. According to Gaspero one type has a completely childish psyche in its total mapping out and in its detailed manifestations, with deficient development of the psychic transformation of normal puberty; the other type has the outlines of a qualitatively normal psychic constitution, but combined with a number of characteristics of childhood; the subjects being half adult and half child, with transitions grading up to the normal. The three outstanding characteristics are the following: (1) The associations are not generalized as in the normal adult but individual and only indefinite; the explanatory associations are subjectively colored. (2) The conceptions of values are childish, the individuals are unable to comprehend big figures of size, space, value and time; they are fond of boundless exaggerations when operating with such figures, and on the other hand underrate objects even of daily use in a childish manner. The patient G. of Peritz, for instance, would buy an umbrella for 35 pfennige (eight cents), one kilo sugar for 1.75 mark (40 cents), a clock for 2 pfennigs (½ cent), and a house in his estimation would cost one million marks. (3) The subjects manifest marked suggestibility. Those examined by Di Gaspero answered persuasive and pressive questions almost always in accordance with the suggestions imparted. This pronounced inductiveness renders infantilism important socially and criminally, since persons thus under the influence of others may readily be made the tools for acts against the law; also their testimony before courts may be entirely valueless or be rated not higher than that of a child. "The psychomechanism renders the individual often a lifelong child; the more so, if also the mimicry, the physiognomy, the gesticulations, the high-pitch and the modulations of the voice remain infantile."

Treatment of Infantilism

The lack of function of one or more endocrin glands suggest the employment of organotherapy. In the thyrogenic forms early and persistent administration of thyroid preparations have proved beneficial as in manifest myxedema. However, also in other endocrino-glandular types it may be tried occasionally with some success.

French authors especially advocated polyopotherapeutic preparations by mouth as well as hypodermatically. Dupuy was the first to apply them systematically, giving simultaneously extracts of thyroid, hypophysis, suprarenals and, in the case of failure, additionally also substance of testes or ovaries. He claimed favorable results. Similarly Marcuse in various kinds of infantilistic states recommends hormin, a preparation consisting of the extracts of testicles, seminal vesicles, prostate or of corpus luteum and mamma in combination with liver, hypophysis, pancreas and thyroid. The stimulating effect of the hypophysis upon the development of the genitals and its successful use in amenorrhea induced Bahrmann, and especially Jendrassik, to administer it in hypogenitalism and infantilism, associated with it. Both authors report good results.

Apropos the experiences with transplantations of glandular tissues and the therapeutic progress made recently in this direction we must refer to the respective chapters on endocrine disturbances as discussed by other authors.

The improvement of the general conditions through organ-preparations is not necessarily due only to a strictly specific action of the substitution therapy; also a non-specific effect, as is known of the protein bodies, plays hereby a certain rôle, namely activation of the protoplasma and a functional stimulation of the entire organism, thus powerfully modifying the nutrition.

In the pancreatic and intestinal types in the first place a proper individualizing dietary management must be directed against the digestive disturbances in accordance with principles detailed in modern text books on children's diseases. In younger children Finkelstein's protein milk may prove beneficial. Preparations of pancreatic enzymes, pepsin, secretin, Takadiastase or hydrochloric acid may find their indications as adjuvants. Holt and Courtney noticed good results from the administration of cod liver oil in connection with proper dietary measures. The therapeutic results from peroral and subcutaneous administration of isolated vitamines as studied recently by various observers in infantile atrophy, hypotrophy and other growth disturbances suggest a trial in selected cases of our field, though no experiences are here extant yet.

Occasionally instances of successful treatment with thymus have been recorded (Wilcox, Kerley, cited by Borchardt).

In dystrophies of luetic origin the antiluetic treatment must be supplemented by organotherapy, the latter being of primary importance as recently emphasized by Hutinel.

However, we must not nurture too optimistic, unwarranted expectations; for in the great majority of cases of infantilism, especially in the unmixed dystrophic types unfortunately hardly any noticeable benefit seems to be derived from any of the known remedies.

SECTION XV

The Endocrine Organs in Their Interrelationships

Multiglandular Syndromes . . . . . *Walter Timme*

Introduction—Definition—Classification—Chief Types of Pluriglandular Insufficiency—Insuffisance Pluriglandulaire of Claude and Gougerot—Description—Etiology—Symptomatology—Progress—Interpretation—Differential Diagnosis—Therapy—Pathology and Pathogenesis—Thymus Suprarenal-Pituitary Compensatory Syndrome (Timme)—Definition—General Description—Symptomatology—Discussion of Symptomatology—Etiology—Discussion of Pathogenesis—Treatment—Endocrine Disorders in Association with Muscular Dystrophies—Historical—Classification—Types Manifesting Endocrinopathic Features—Onset, Symptomatology and General Course of the Disease—Treatment.

Multiglandular Syndromes

WALTER TIMME

NEW YORK

Introduction

Definition.—*Multiplicity of Features.*—When one considers the interrelation and interdependence of the units of the internal glandular system it is hardly conceivable that there should be any absolutely uniglandular disturbance. And so it becomes necessary to offer some explanation that the title of this chapter is designed to cover only a very limited portion of the many endocrinous conditions. It is much more simple to do this than to offer a formal definition of the term "pluriglandular disturbance" as distinct from "uniglandular disturbance." And so let it be agreed at the outset that by *uniglandular disturbance* is meant such a pathological condition as may be produced by the disturbed activity of a single gland primarily, however many of the other glands may be called into subordinate play; but furthermore that the resulting syndrome be composed almost entirely of the manifestations of this particular gland's dysfunction, overshadowing the effects of the disorders of the subordinates. Addison's disease and myxedema offer examples of this type. Exophthalmic goiter is usually considered also as of this class, although the evidence of late years is gradually assigning it to the pluriglandular group of endocrin disorders.

A *pluriglandular syndrome* might then be stated to consist of a group of symptoms and physical signs produced by disturbances of the glands of internal secretion in which either synchronously, alternately or consecutively, the manifestations of the various disturbed units make their appearance.

The whole aspect of multiglandular syndromes is more or less confusing at the present stage of our knowledge. If the disturbances in one gland are accompanied practically always by disturbances in all the others, why is it that these secondary manifestations, providing the initial gland is the same in every case, are not always similar and that the resulting picture is not always more or less in conformation to a type? Why is it that a diabetic mother should give birth to a child with exophthalmic goiter

in one instance and at another time to a child with status thymicolymphaticus? Why should the ablation, by surgery, of the thyroid, frequently be followed by hypertrophy of the pituitary, but occasionally not at all? Following this reasoning as applied to whole families through several generations, why should union of two endocrinopaths result in many diverse types of endocrin disturbance through successive generations, whose various members seldom transmit the identical disease entity they themselves possess?

An illustrative chart of endocrinopathic heredity is here given.

Examining this chart, we see that through four generations, beginning with the union of a moderate giant and a diabetic, the greatest diversity

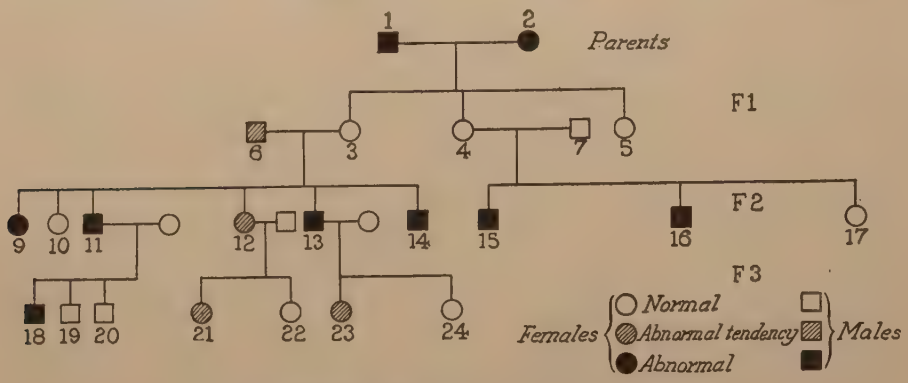


Chart Showing Endocrinopathic Inheritance

1. Giant.
2. Diabetic
6. Dyspituitaric
9. Exophthalmic Goiter
11. Harelip
12. Dyspituitaric
14. Congenital Blindness
15. Moderate Giant
16. Giant
18. Osteomalacia and Dwarf
21. Hyperpituitaric

of endocrinopathic inheritance is manifest. Gigantism, exophthalmic goiter, dwarfism, hypothyroid state with infantilism, and dyspituitarism are all encountered. Is it not reasonable to suppose that those states represent the attempt of the individual to counterbalance the odds that have been laid against him in the transmission of a condition which if persistently transmitted, would bring the stock to an end? It is this struggle against a stock deficiency that brings latent possibilities and potentialities to the fore, and makes for the survival of the individual. So must we have individual pluriglandular disturbances as well as stock pluriglandular manifestations. And so arise the traits and reactions and adjustments of each unit of the family, making of such unit an individual different from all others (Timme (*a*), 1916).

Noël Paton says, "When studying the action of the testes and thymus on growth, I found that one guinea-pig in my series, after removal of the

thymus, hardly grew at all, although remaining quite well and active. When it died at over four months old it was like an animal about a fortnight old, and the testes were in size and structure those of an animal of the same age. They had undergone no compensatory hypertrophy, as they usually do, and the result had apparently been the arrest of growth which occurs when thymus and testes are removed together." In other words, removal of one of the endocrin glands is not necessarily followed by the same sequence of events in every case. The realization of this state of affairs accounts for the diversity of opinion and difference of conclusion of various observers pursuing similar lines of investigation. It apparently contradicts the laws of logic and mathematics. But only apparently. For the basic difficulty is that in mathematics one must have two equations to determine two unknown quantities that have functional relations with each other. In experimentation upon the endocrin organs, the gland the function of which is to be determined is balanced against the whole remainder of the system—all unknown and variable quantities—as the second unknown quantity. Here is the error—for the remainder of the system is not one constant but many independent variables; and being such, the value of the gland experimented upon can never be determined in terms of the others, or of any constant. Hence also, the perturbations of one gland, operating functionally in one human being can practically never be accompanied or followed by the same chain of events in the other glands in him, as in a second individual—unless in the almost infinitely small chance of two beings having the variables—the endosecretory glands—varying mutually and respectively alike.

This gives rise to manifestations, in different individuals with similar original gland disturbance, of clinical pictures which may vary only in degree; or if this degree becomes so great as to be critical, then also in kind.

As a result, the so-called pluriglandular syndromes are of necessity not clearly demarcated and sharply separated from one another, but merge imperceptibly into one another; and furthermore, within the limits artificially set for any one of these syndromes, there appear frequently single instances of so-called uniglandular involvement such as exophthalmic goiter, acromegaly or Addison's disease. However, within the limitations imposed by any one syndrome it will be found that many individuals can be grouped with much similarity in their symptomatology. As the limits are approached, the number of cases grows larger, the symptomatology gradually changes, many connecting links are either not seen or else not reported and gradually this syndrome merges into another more or less well defined group—which again may be designated by the term syndrome.

Classification.—Theoretically, the various pluriglandular syndromes might be classified in a manner which would conform to the following groupings:

1. Uniglandular syndrome with secondary or subsidiary pluriglandular manifestations; e. g., myxedema, Addison's disease.
2. Transitional groups. Fröhlich's dystrophy.
3. Pluriglandular insufficiency syndromes (Claude and Gougerot).
4. Pluriglandular hyperfunctioning syndromes; e. g., hyperthyroidism with hyperadrenalism.
5. Pluriglandular compensatory syndromes; e. g., thymus-adrenal-pituitary type (Timme).
6. Pluriglandular antagonistic syndromes; e. g., combinations of myxedema and exophthalmic goiter.
7. Syndromes frustes.

For the present, it perhaps is wise to confine the discussion to the two more or less well defined large classes—pluriglandular insufficiency and pluriglandular compensation. A consideration and study of these will give the reader the salient features of pluriglandular disturbances in general. The remaining classes above given will be discussed under the separate chapters devoted to the particular glands involved and it would be supererogatory to include them here. The syndromes frustes need no particular attention. In general, however, it may be said that the pluriglandular syndromes are as yet but very poorly understood. Knowledge in this department is as yet at its very beginning. Longer experience and more exact analyses will be required to illuminate this domain. Ideas presented here are current at present but may undergo great changes later as endocrinology advances.

Chief Types of Pluriglandular Insufficiency

1. Insuffisance Pluriglandulaire of Claude and Gougerot

Description.—Perhaps the most widely recognized of the pluriglandular syndromes is that known and termed by Claude and Gougerot (*a*)(*b*) as pluriglandular insufficiency. Under this heading these writers describe a condition in which more or less simultaneously various glands of internal secretion gradually undergo atrophy and the manifestations of their deficiency become part of a clinical picture. This clinical picture is subject to the greatest variations depending upon such factors as the intensity of the process on the several glands, the degree of compensatory possibilities and the natural resistance of the patient. So that in combination with gonadal disturbances we may get Addison's suprarenal disease, or myxedema or a combination of acromegaly with exophthalmic goiter; in short, practically any combination of a deficiency character.

Etiology.—By far the greatest factor in the etiology is the hereditary one, predisposing the individual to the development of the syndrome as a

result of various exciting final causes. The basic constitutional predisposition can occasionally be recognized even before the actual process has set in. The suspected individuals usually show in adolescence a late development of their gonadal activity. Women menstruate late; males have a delayed puberty with little sexual appetite. Both sexes are disposed to be asthenic. The final factor that ushers in the atrophic process may be of quite moderate significance for normal individuals, such as malaria, excessive use of tobacco (Hertoghe), or pregnancy; but usually the final cause is of rather severe nature, namely, the acute infections, influenza, scarlatina, measles, diphtheria, acute articular rheumatism; or the metallic poisons, lead, arsenic, mercury. Alcoholic and drug habitués are also prone to be affected. Occasionally the syndrome is engrafted upon a previously existing cirrhosis of the liver. Possibly the most frequent causes, however, are syphilis and tuberculosis (Poncet and Leriche; Faneau de la Cour). Besides chronic malaria, leprosy and pellagra have been cited as causative factors (Agostini). In spite of this comparatively long list of inciting causes, it is only in a surprisingly small number of individuals that the sequel of a pluriglandular insufficiency becomes manifest. The probability is great that these diseases are not specific in their selection as far as the ductless glands are concerned, but act simply as final critical determinants upon a system already weak or in unstable equilibrium through inheritance or through lack of compensatory possibilities in the system beyond a certain quite limited range. Such an organism might go on seemingly normally for an indefinite time were the limit not transcended. But the "call" or "drag" made especially upon such of the glands as the thyroid or suprarenals by acute infections or intoxications is too much for the small margin of safety allowed by the inefficiently resisting organs and the pluriglandular disturbance then begins its insidious course. Traumatism may also play either a primary or secondary rôle in the production of the syndrome; primary, if through the trauma one of the endocrin glands is directly injured to such an extent that it cannot meet its physiological requirements, as in traumata of the testicles or the suprarenals; secondary, if general bodily injuries are of such extent and productive of such shock as to require more of the protective and stimulative secretions than can readily be supplied without producing exhaustion of the glands beyond the possibility of their complete restoration to function.

It can readily be surmised that with so great a latitude of incidence and with such variability of individual glandular reactivity to noxious agents, all conceivable combinations of clinical pictures are possible, once the disease process has begun. And so various groupings, depending upon the particular series of glands most obviously affected, are described by various authors all merging, as before stated, into one another. Such groups are the gonads, thyroid and hypophysis; gonads, suprarenals, para-

thyroids; thyroid, testicles, hypophysis and suprarenals; thymus, suprarenals, hypophysis; and so on almost indefinitely.

Symptomatology.—The syndrome develops between the ages of 25 and 30 years and is more frequently seen in males than in females. Up to this age sexual and genital development are apparently normal or only moderately delayed. Indeed, some of the patients may have already married and borne children. After the particular etiological factor has arisen, the patient begins to suffer from fatiguability after exertion which theretofore never produced fatigue. This occurs both in the muscular and the mental spheres. Or else, one of the tissues such as the hair shows the atrophic process and begins to fall out. In still other cases, the sexual appetite diminishes and impotency arises. Again, the symptoms arrange themselves about the gastro-intestinal tract and we see nausea, vomiting, anorexia, with loss of weight, some discoloration of the skin with thickening of the epidermis. This condition may last for years. The patient shows a face free of hair, pale, dry and of a yellowish brown color. Occasionally there is a myxedematous condition of the lower lip which looks puffy and thick and becomes more or less protruded. The skin of the body is generally thick, dry and scaly, but usually whitish and translucent in contrast with the pigmentation of the face. The genitals are small, the scrotal sac is without tone and the testicles are extremely small. The thyroid gland is regularly small. The limbs are flail-like and the rounded muscle contour gone. There are no acromegalic features in this syndrome though the epiphyses are united. With the weakness, a certain degree of lassitude and apathy are manifested. The patient cannot bear cold and has the constant subjective sensation of cold. Mentally the picture is one of instability—irritability and anger arising from the merest trifles and ideas of reference developing occasionally. A lack of inhibition is manifest. In those cases in which the syndrome arises soon after puberty, the voice becomes high-pitched. Polyuria and polydipsia are frequently met with. Diarrhea and progressive gastro-intestinal disturbances occur. The pulse becomes slow and the blood pressure low. Spasticity of the blood vessels occurs with resulting acroparesthesia and erythromelalgia (Murri). Here the syndrome frequently merges into the Raynaud type. The teeth frequently fall out and those that perchance remain are carious (Sourdel). Headaches and neuralgic pains in the extremities and elsewhere are common. Frequently they are so intense as to prevent sleep. While no actual muscle atrophy is seen, yet tetanoid muscle spasms are met with. The reflexes are unaltered with the exception of the cremasteric which is diminished. Hyperacusis and tinnitus also occur. Nasal hydrorrhea has been noted. Smell is usually diminished and frequently vanishes. Physical and psychical impotence are important observations. Blood examination frequently shows a leukocytosis and an eosinophilia.

Progress.—The progress and evolution of the syndrome are usually protracted over a number of years. Frequently an intercurrent disease determines a lethal end; usually this disease is of infectious character—tuberculosis offers the best example. The natural resistance of the organism to such infection is markedly diminished and the course of such intercurrent disease is usually rapid. Unless such interruption occurs, the gradually increasing asthenia finally determines the outcome. Drowsiness becomes more and more prominent, the progressive weakness necessitates complete rest in bed, the bed-ridden patient sinking lower and lower gradually, until finally he dies. There are, however, exceptions to this termination. Occasionally, as described by Cordier et Francillon, remission occurs even to the point of recrudescence of libido. Byrom Bramwell likewise reports improvement in the genital sphere in one of his patients. The disappearance of some symptoms, however, frequently ushers in the appearance of others. Thus Sourdel describes the appearance of diminution of vision and hemeralopia with the disappearance of the genital symptoms and the reappearance of hairy growth. In women, a usually prominent accompaniment is a disturbance of the menstruation. Frequently the menopause ushers in the syndrome. As in men, the loss of hair is of note, but is frequently followed by the appearance of a moustache. The breasts become atrophied. A subsidiary form of the syndrome presents changes in the pigmentation of the skin combined with symptoms of exophthalmic goiter and eunuchoidism. Such types are reported by Sourdel, Levi et Rothschild, Faure-Beaulieu, Villaret and Sourdel. The secondary type occurs usually in the wake of an infectious disease, beginning with headache, dizziness, and loss of hair especially marked in the secondary sex regions. With these tissue changes there occur also changes in the mental level. The patient becomes irritable, depressed, and self-centered. Alternate boulimia and anorexia are exhibited. Coincidently, the disturbances in the skin become apparent. Brownish patches such as are seen in Addison's disease develop. Patches of vitiligo with sharply demarcated dark brown borders are frequently seen, especially on the abdomen. With the disappearance of the secondary hairy growths, the breasts atrophy, and possibly exophthalmos with a slightly enlarged thyroid makes its appearance. Following closely upon this, tachycardia with cardiac dilatation arises. Vomiting and diarrhea assist in making the patient miserable. Libido vanishes. Asthenia supervenes. There is frilosity with alternate colliquative perspiration. During this development, the blood pressure goes lower and lower and death at last brings relief. The development is much like the Addisonian, but much slower. Still other sub-types, in which, together with the myxedematous characteristics of the above, there are combined disturbances pointing to involvement of the pituitary gland, with genital and gastro-intestinal accompaniments, are described by various observers (Brissaud and

Bauer, Collard-Huard, Cordier and Rebattu, Renon, Delille and Monier-Vinard).

Interpretation.— In the variegated pictures presented by this syndrome it is possible with a fair degree of accuracy to base the deficiency symptoms upon the diminishing activity of special glands. Thus, the disappearance of the secondary sex characteristics and the libido may be attributed to the atrophy of the gonads and interstitial cells, and possibly the suprarenal cortex. The loss of hair on the scalp, the changes in the teeth and many of the other trophic disturbances together with the accompanying psychic disturbances may be traced to thyroid insufficiency. It may be doubted, however, whether the myxedematous characteristics can be wholly credited to the thyroid disturbance, for the administration of thyroid extract does not serve to eradicate them entirely. The polyuria and generally cachectic condition are probably hypophyseal in origin, while the pigmentation, hypotonus and asthenia are the result of suprarenal involvement (Wiesel (*a*) (*b*)).

Differential Diagnosis.—*Myxedema.*—While true myxedema is more or less of an entity, the myxedematous characteristics of this syndrome form only part of the picture and arise secondarily and much more slowly than in pure myxedema. Furthermore, women are much more prone to myxedema than men, whereas men are more frequently the victims of this multiglandular disturbance. The nervous and mental symptoms in true myxedema are much more pronounced and characteristic and dominate the picture to a far greater degree than in this syndrome; while the genital disturbances are much less in evidence. The blood picture also differs in the two conditions. The leucopenia with a relatively high lymphocytosis seen in myxedema does not occur in this syndrome. The fact that the administration of thyroid gland is only partially successful in combating this syndrome compared with its striking results in pure myxedema is also of great differential value.

Addison's Disease.—While pronounced pigmentation occurs in both conditions, yet the disturbances of the hairy growth are almost never seen in Addison's. Also, the rapid course of Addison's disease finds no counterpart in this syndrome, the asthenia coming on much more slowly.

Dystrophia Adiposogenitalis.—No hypophyseal tumor is to be demonstrated in the pluriglandular syndrome.

Infantilism.—In this condition, the body is small, the bony structure is delicate, while the head is of normal size. In the pluriglandular cases, there is no body disproportion and the appearance of senility in them finds no counterpart in infantilism. The genitals do not resemble those of children—as being undeveloped—but are developed structures which have undergone atrophy.

Thymus-Adrenal-Hypophyseal Syndrome (Timme). In this condition the process begins in infancy or very early youth and is based upon a

presumably disturbed thymus function, as contrasted with the syndrome under discussion. Myxedematous characteristics practically never appear, and falling out of hair is not recorded. There is deficiency of hair ab initio. The thymus-adrenal-hypophyseal syndrome is a more or less compensatory one, the patients after a protracted siege, extending over one or more decades, going to cure, as contrasted with those under discussion who become progressively worse and in whom treatment is only of partial avail in slowing the process.

Therapy.—As is indicated throughout the discussion of this disease process, therapy is only of partial avail with but temporary effect. Thyroid administration serves to mitigate the myxedamatous symptoms. Mixed glandular therapy of course in all degrees and combinations has been attempted, with but little reported success. Serum of thyroidectomized goats has been said occasionally to effect some improvement.

Pathology and Pathogenesis.—A number of cases of this pluriglandular insufficiency have come to autopsy (Sourdel). With great uniformity, there have been found in the glands suspected clinically processes of connective tissue hyperplasia—scleroses—findings that explain their dysfunction during life. The glands implicated were chiefly the thyroid, gonads, hypophysis and adrenals. The sclerosis determined a definite functional lack, for large areas of the parenchyma of the several structures had degenerated. In the thyroid, frequently tuberculous nodules with connective tissue proliferation were seen. Occasionally in liver and pancreas also a chronic interstitial productive inflammation was manifest. Many theories of course endeavor to account for this connective tissue diathesis. Wiesel believes that possibly one particular gland bears the same relation to this interstitial process as does the pituitary to fatty deposits, and that this gland is in all probability the thyroid; for, as in our experience cirrhotic processes are never seen in hyperthyroidism, their presence in subthyroid activity argues strongly for the contention that thyroid deficiency must bear the responsibility for their production.

2. Thymus-Suprarenal-Pituitary Compensatory Syndrome (Timme)

Definition.—This syndrome differs from the pluriglandular insufficiency of Claude and Gougerot. For, although in the latter remissions and stationary stages are described, the various subtypes of the pluriglandular syndrome of Claude and Gougerot are all progressive. The general evolution of the disease is characterized by the downward tendency of the patient towards death through progressive asthenia or intercurrent disease. The syndrome now to be described is one that only exceptionally follows a downward course even though its activity is manifested throughout several decades. While absolute recovery in the sense of a full restora-

tion to normal health is not usually to be looked for, yet the recovery is more or less complete except for some moderate limitations that prevent excessive activity and energy expenditure. The syndrome was originally described in 1918 by Timme (*b*).

From observations and clinical examination of many patients over a period of seven years he came to the conclusion that certain types of endocrinopathies, such as status thymicolymphaticus, giantism, infantilism, acromegaly, and many others, are not static states, as one would be led to suppose from descriptions in the literature, but are simply cross-sections taken at intervals in a dynamic, progressive, and widespread disturbance of the internal glandular system. The constant repetition of the appearance of patients in his clinic showing similar symptoms and similar physical signs which theretofore had been generally accredited to the asthenias accompanying neurasthenic and psychasthenic states was noteworthy. The patients were usually of the late adolescent period, in the early twenties, and, to neglect for the present the detailed symptoms, the outstanding complaints, overshadowing all others, were headache and muscular fatiguability. Accompanying complaints of these two suggestive symptoms there was an additional statement that they had been growing very rapidly for the preceding few years. Going deeply into their antecedent history and their family history one was able to find many points of resemblance in these various individuals. One case, observed for six years, went through various stages to recovery at the age of thirty-two years. From his early history symptoms were recognizable that are presented by cases in the beginning stages of this syndrome, notably the headaches, fatiguability, and the skeletal overgrowth. Cross-sections at various stages of his further progress also resembled clinical pictures in patients that had formerly been somewhat puzzling to analyze.

During the past few years so many cases of a similar nature had been observed that from past experience it was possible to foretell, to a degree, the progress such cases would make. To add to this assurance, Timme had seen many patients admitted to the hospital for divers complaints of middle age, in whom he could recognize the final compensatory stages of this syndrome. Upon close questioning, their antecedent history bore out the facts that his studied clinical types presented in various stages of the syndrome. They were completely compensated cases and their presence in the hospital was due to some entirely adventitious cause. Observation to the present time has disclosed: (a) clinical types presented by single cases at various ages and stages of the syndrome; (b) progressive cases, observed over periods of from one to six years, which showed the changing and probably compensatory nature of the disturbance; (c) completed cases in which the disturbance had come to a definite stop, in which the antecedent history revealed the close relationship to the isolated cases which were still in active progress; (d) uncompensated cases in which the

condition, after passing through the preliminary stages, remained indefinitely progressive. It has been impossible, as yet, to observe one case from the beginning to the end of the syndrome—a period which varies from ten to twenty years—and until this can be done we must fill in the gaps as best we may.

General Description.—This new syndrome, pieced together as described above, may be generally stated to begin in youth some years before puberty, and go through its varying stages in about twenty years. In its incipiency (*first stage*) it presents largely the characteristics of the so-called status thymicolymphaticus, or status hypoplasticus of Bartels. There is complaint of muscular fatiguability as a subjective sign with frequent accompaniment of headache. Objectively the case presents usually, though not invariably (for exception see Fig. 5), an insufficient genital development, with perhaps inversion of sex type, with a penis that emerges from scrotal folds of labial type, or cryptorchism, or both. In the female the menses are usually delayed, the uterus and ovaries remain infantile, and there is scarcity of pubic hair. Blood pressure is usually low and blood sugar content low. Enuresis is common. There is usually present the white line of adrenal insufficiency of Sergent.

In the *second stage*, that beginning at puberty, we find a continuance of the muscular fatiguability or even an increase. The genitals may remain backward or inverted in development, the pubic hair is sparse and has the distribution of the opposite sex, the male showing a horizontal demarcation, while the female has the pyramidal type in which the middle line to the umbilicus shows a hairy tendency. Axillary hair is absent and chin and lip show no signs of hair in the boy. Blood sugar is low, usually below 0.07 per cent, and the blood pressure is below the normal. The white adrenal line may be elicited, especially marked after fatiguing exercise. Röntgenograms of the skull usually show a sella turcica which is small or which may apparently be even enclosed by the clinoid processes. This is an important point to determine, for the later progress of the disorder presumably depends upon the capacity of the pituitary gland to become enlarged. The size of the sella turcica, therefore, plays a determining rôle in the production of the later symptoms. The possible excessive function of the pituitary later on dominates the picture and is conducive to compensatory cure. The thymus gland frequently is seen in the *x*-ray picture as quite enlarged. In some cases of extreme fatiguability there are also seen pineal shadows. During the second stage rapid growth in length begins to become manifest—not ordinary normal growth—but rapid in the extreme, so that five or six inches increase in height a year is frequent. With this growth fatiguability increases, and it is usually on this account that the patient is first brought to the physician.

In the *third stage* we begin to see the results of some of the compensatory activities. It is usually ushered in about the twentieth year of

life. Growth has continued until the patient is six feet tall or over; his weakness, even though his musculature seem splendid, is his prominent symptom. He shaves rarely or never. Pubic and axillary hair remain as before. Now he begins to notice an enlargement of his hands and feet, and a frontal headache or, rather, an intratemporal headache appears. Blood pressure remains low (90 to 100 millimeters, systolic); blood sugar usually remains low, but now frequently rises as compensation progresses. The patient shows decided vagotonic symptoms. An *x*-ray of the skull at this stage, or during this stage, if the case progresses favorably, shows a sella turcica which, while small, may show erosion of the clinoids and a deepening of the cavity. This tendency of the pituitary to become hyperactive produces the headache (if the sella is contracted), the increase in blood sugar content, the growth of hands and feet, and a gradually rising blood pressure. Where the sella is roomy, the headaches are usually absent.

Fig. 1. Shows abnormal length of thorax compared with legs. Thighs especially short compared with lower leg. Small genitals. Has large thymus and enclosed sella. Represents status thymicolymphaticus condition, from which springs the syndrome.

The *fourth stage* is entered from three to ten years later. This is the stage in which either complete compensation is produced or else the untreated case takes on the varying and various attributes produced by an enlarged pituitary body engrafted upon the earlier manifestations of a thymic state. That is, we have in the completely compensated case features of acromegaly, although the blood pressure and blood sugar are normal and the headaches have gone. The sella turcica on *x*-ray examination seems large. In the uncompensated cases we usually see a sella which is still small and perhaps bridged, with headaches of increasing severity, perhaps attacks of petit or grand mal, dependent upon the disturbance of pituitary function, mental torpor, increase of weight with constantly increasing fatigue, and a final lethal termination due to intercurrent disease.

Symptomatology.—*Résumé of Essential Features.*—A brief résumé of the characteristic symptoms and findings in the different stages is here given.

First Stage.—The bodily structure shows various anomalies and defects: disproportion of various skeletal units; teeth late and usually characteristically anomalous, so that the lateral incisors are very small, the central incisors disproportionately large, the canines of the type of incisors with a cutting edge instead of a tearing point; epiphyses slow in joining shafts of bones; hyperextension of joints; hair growth late and sparse; cramps in muscles; tendency to hemophilia and spasmophilia; enlarged

Fig. 2. Sella turcica small and entirely enclosed and "roofed in." It is the ability of this sella to enlarge which determines the later, successful compensation.

thymus; maxillary torus; tonsils large and adenoids present; cyanosis of extremities; fatiguability; small sella turcica; enuresis; low CO_2 coefficient of the blood. Figs. 1, 2, 3.

Second Stage.—This begins at about the age of puberty; rapid skeletal growth takes place; the menses are late and the uterus is small or infantile; There is great fatiguability with evidence of a low adrenalin supply—low blood sugar; low carbon dioxid combining power of the blood; white line of adrenal insufficiency; the pubic hair is of inverted type; there is lack of hair on the face and chin and in the axilla; the skin is smooth and soft like that of a child; the genitals are of inverted type or else there may be vagotonia with symptoms of hyperacidity and gastric ulcer; enuresis may be present; undue length of long bones; low blood pressure; little stamina; mentally, there is lack of initiative and concentration.

Third Stage.—Twentieth to thirtieth year; beginning gigantism mani-

fests itself; headaches, pituitary in character come on; there is drowsiness; acromegalic beginnings or other pituitary stigmata may be seen; the fatiguability may continue or lessen; there are mental confusion and hebetude; epileptiform attacks may occur, uncinate in type; the sella turcica enlarges or else erosin of sella or clinoids takes place; the blood sugar

Fig. 3. Shows thymic enlargement. Arrows point to margin of thymic shadows.

gradually increases if a cure is established. In uncompensated cases mental symptoms, moral and intellectual deficiencies and delinquencies arise.

Fourth Stage.—Either complete compensation is reached, so that the patient may live comfortably within limits of exertion, or else the condition may progress to the end of life as a pituitary case. The various external manifestations of pituitary disturbance remain even if the physiologic cure is complete. The blood pressure rises; the headaches cease; the fatiguability vanishes.

Discussion of Symptomatology.—The bony structure in the first and second stages usually shows anomalies in proportionate skeletal growth,

i. e., legs too long for thorax or vice versa. The scale for this determination is a fraction with the numerator as the distance from the sternoclavicular junction to the anterior superior spine of the ilium of the same side, and the denominator the distance from the anterior superior spine to

Fig. 4. Age thirteen and a half years. Shows hypoplasia of genitals and a scrotal fold surrounding base of penis. Absence of hair. Bruise on raised arm from slight pressure. Represents the second stage of the syndrome with headache and fatiguability. Pathological liar.

Fig. 5. Feminine distribution of pubic hair: large genitals; height 6 feet, 1 inch. No hair on face. Seems well proportioned. Low blood pressure; low blood sugar; headaches and fatiguability. Represents transition from 2nd to 3rd stages of syndrome.

the external malleolus; normally, this fraction is one-half—a larger one meaning too large a torso, while less than one-half represents too long a leg; this is the torso-leg ratio. The joints are usually hyperextensible and frequently the ligaments are so relaxed that dislocations are easily produced. The extremities can be thrown about like flails. While the teeth

are usually delayed in their appearance they also show certain characteristic anomalies. The lateral incisors, especially in girls, are frequently greatly underdeveloped. The canines, likewise, are either underdeveloped or else take on the flat appearance of incisors, losing their fang-like appearance. With the cyanosis of the extremities we occasionally get a pustular-like eruption about the nails. The symptoms during the second stage may need some elucidation. The so-called "white line" of adrenal insufficiency was first described by Sergent. It has not been proved to be due to the deficiency, but in my experience it invariably accompanies fatigue

Fig. 6. Shows sella turcica of patient Fig. 5. Complete closing in of pituitary fossa by massive clinoids.

states, and may be made to disappear very quickly after a hypodermic injection of epinephrin. Previous emotional disturbance, even so slight as that produced by standing before a camera to be photographed, will make its appearance impossible to obtain. It is obtained best by having the patient lying quietly in bed for a short while and then stroking the skin, preferably of the abdomen or thigh, lightly with the palmar surface of the index finger. In ten to twenty seconds there will be a blanching of the skin thus stimulated. (See Sergent's article, 1917, for the explanation of this phenomenon.) The low carbon dioxid combining power of the blood plasma diminishes the so-called "buffer" property of the blood and leads to acidosis on slight provocation. The smooth soft skin of these patients, even in the third decade of life, with little or no secondary hair on the face, a faint suspicion of lanugo on the lip and chin, and a "peaches and cream" complexion, frequently stamp these cases at sight. The head-

aches, produced as will be discussed in the pathogenesis, are of a specific type. They are invariably stated to be between the temples, the patient indicating the locality by putting one index finger on each temple, directed mesially. We have come to call them "pituitary headaches." The vagotonia present in many of the cases frequently takes on the character of hyperacidity of the gastric juice with frequently symptoms of gastric ulcer, spastic constipation, and eosinophilia. In the third stage the symptoms of great interest are the mental. In many years' observation of pituitary disorders we have been frequently struck with the mental quips of the hypopituitaric. He exhibits lack of inhibition of the emotions, becomes highly excitable on little cause, alternating with sluggishness; frequently has phobias and compulsions (one case was a true kleptomaniac), shows frequently moral and sexual obliquities; and exhibition of pituitary

Fig. 7. Height 6 feet, 2½ inches; feminine pubic hair; no hair on face; musculature seems flabby; feminine attributes. Blood sugar and blood pressure still low, with headaches markedly diminishing. Represents 3rd stage of syndrome.

Fig. 8. Result of treatment of patient Fig. 7. Masculine pubic hair and hair on thighs. Patient is now also growing mustache and beard.

feeding often modifies these characteristics. The symptoms of the uncompensated cases usually merge into those of a frank dyspituitary syndrome. Blood sugar disturbances, intense fatiguability, periodic headaches, temperamental unfitness, and drowsiness are among the prominent symptoms.

Fig. 9. Height 6 feet, 2½ inches. Fully compensated case. Great length of leg compared with length of thorax. Feminine pubic hair; feminine waist; hands of giant type; no hair on face. Able, after many years, to resume efficient work. 4th stage of syndrome.

Etiology.—In practically all of our cases there have been family histories of importance as regards endocrinopathies. Frequently parents or grandparents have shown such disturbances as diabetes, goiter, or acromegaly. A very common complaint is gigantism. Collateral branches, too, show similar disturbances. Thus, W. W. (Fig. 9), the fully compensated case, has four cousins all afflicted with Graves' disease. There appeared in our cases no particular antecedent disabling disease or injury. One patient, now in the second stage, had two brothers, both dying suddenly after exertion without known cause, in youth—possibly a so-called thymic death. Periodic headaches are also distinguishing marks. Menstrual disturbances of all kinds are met with here, chiefly the late-appearing type with lack of periodicity, almost invariably delayed.

Discussion of Pathogenesis.—During the first stage we see a clinical picture which is dominated by the characteristics of the status hypoplasticus of Bartels. The anomalies have been variously credited to hypofunction of the individual endocrin glands, excepting the thymus, which is supposedly hyperactive. Thus, Tandler and Grosz, and Tandler have described many of the features of such a condition due to deficiency of the gonads. And yet, in direct contradiction to their view that gonadal deficiency produces growth in height with late joining of the epiphyses, cases have been seen in which, for example, at the age of eighteen with no menstrual flow yet established, the sexual apparatus quite infantile, the skiagram of the long bones showed the epiphyses almost united, the height of the patients being under five feet (personal observation). Wiesel, Schur, and Schmorls and Ingiers have given both clinical descriptions and

histologic and pathologic findings in such hypoplastic conditions referable to underactive or inhibited suprarenal glands. Many observers have described the smallness of the sella turcica. Timme's observations agree with these. All of the cases show the smallness of the sella turcica in the early stages and, in addition, many of them have the bridging over by the clinoid processes, evident on *x*-ray examination. With these deficiencies of glandular structure and their diminished potential physiologic activity from the outset, the organism would of necessity come to early grief if some corrective were not forthcoming. Many patients do succumb early. Undue exertion, sudden excitement, narcosis, are all critical moments for such organizations, many of which cannot survive them. After puberty should have been reached (the second stage) the deficiency of the gonadal inhibition to growth (Tandler and Grosz) is claimed to be responsible for the extreme height rapidly reached in these cases. One of the patients (Private B., Fig. 5), however, rather opposes this theory, in that the gonadal system early became hyperplastic and still the growth in body took place. This excessive genital development may be due in his case to an early involution of the pineal gland, for in the *x*-ray calcification of the pineal is seen. (Some authors hold that the overactive thymus with disturbed calcium metabolism is the cause of such "thymic gigantism.") The deficient adrenal-chromaffin system is to be credited with the great fatiguability, the low blood sugar content, the low blood pressure and the white line. Now comes the third stage, the all-important one. It is in this period that the outcome of the syndrome is determined. In our judgment it is the pituitary gland which is here the critical factor. As we have seen, it is invariably enclosed in a small sella turcica and possibly even hemmed in by the clinoids. Among its functions we have as all important a blood pressor principle and a sugar mobilization factor. Both of these are deficient in our patient. If the pituitary possibly could become hyperplastic and hyperactive with an intensification of these important properties, compensation might be accomplished. Such tendency to hyperplasia in a small cavity would of necessity, through pressure, produce headaches—an invariable symptom in the third stage of the compensated cases. And such headache would continue until the enlarged gland through erosion of its bony capsule or through pushing apart the clinoids made sufficient room for itself. As will be seen, these headaches continue for two to ten years in some of the cases. Synchronously with these headaches, other incidental features of an enlarged pituitary gland become manifest: (a) acromegaly, developing until the headaches cease and the process then likewise ceasing; (b) a higher blood sugar content; (c) a higher blood pressure; (d) a diminished sugar tolerance. To make this view of the nature of the process of compensation more tenable many of the sellæ turcicæ of the patients in the second and third stages show

erosion of the anterior or posterior clinoid processes or the floor or dorsum of the sella; and in the final stage, an enlarged sella with practically no clinoid processes left at all. In the cases in which no compensation is effected—i. e., in which fatiguability and the other symptoms remain and progress—the sella shows no enlargement (notably that of T. R., Fig. 10). It is necessary to be cautious in the interpretation of sellar changes and a safe method would consider only the grosser changes. In these cases there are headaches, periodical in type, adiposity, mental and moral deficiencies, petit mal, and other manifestations. Curiously enough in all cases, the feeding of pituitary gland in fairly large quantity disposes

Fig. 10. Uncompensated case. Age thirty-five years; height 6 feet, 1 inch. Sella turcica completely shut in and extremely small. Confirmed by stereoscopic plates. Intratemporal headaches; adiposity; moral lapses; pathological liar. Much improved by treatment.

of many and at times of all these symptoms. But if the feeding is diminished or stopped, the symptoms reappear. It seems analogous to thyroid feeding in myxedema. One case, which gives a typical early history and seems uncompensated to-day at the age of forty-four, still shows the very small sella turcica with a clinical picture of abnormal bony structure much resembling Paget's disease. On pituitary feeding, this case is improving markedly in its features of fatiguability, headaches, and heaviness of extremities. Finally, the fourth stage is ushered in by a gradual cessation of the fatigue, amelioration of the headaches, restoration of a normal blood pressure, and normal sugar content of the blood. But the adventitious signs of the disturbance of the pituitary gland remain. Thus the fully compensated cases may show acromegaly more or less marked; *and this acromegaly is not to be taken as a diseased condition needing treatment, but simply as the hallmark of a process that has come*

to a stop—a self-curative process. It is analogous to the hypertrophied heart, become so through the deficiency of the cardiac valves and making up for such deficiency by its enlargement. And that condition likewise, per se, needs no treatment. A case that presents acromegalic features, therefore, need not necessarily be a case that calls for therapeutic intervention. It may well be a "finished" case. W. W. (Fig. 9) is a good representative of this type. In these "finished" cases the patients must always, however, live within certain limits of exertion and stress. The

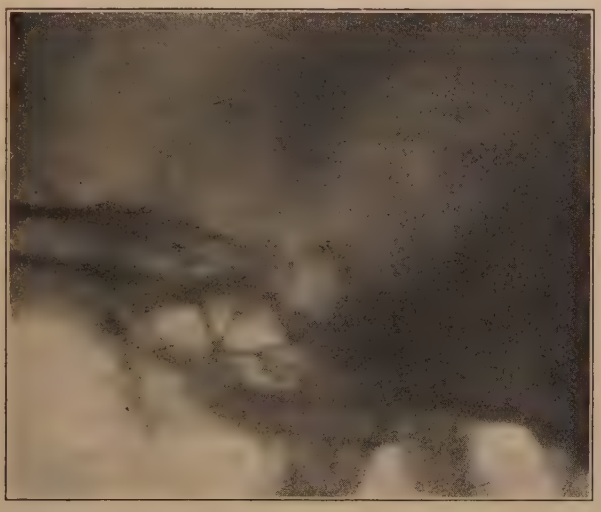


Fig. 11. Uncompensated case. Shows pituitary fossa completely enclosed. Stereoscopic plates confirm this. Girl, age twenty-two years; height 6 feet. Inability to walk a short distance; headaches severe. Low blood sugar; systolic blood pressure 90.

cases that in the fourth stage do not spontaneously go to full compensation are those in which we either find a sella turcica which did not enlarge (perhaps because there was no spontaneous effort of the pituitary to become hyperactive) or in which an enlargement of the sella did take place and the pituitary even in its hyperactive condition was not sufficient to compensate. These uncompensated cases go right on with progressive symptoms of fatiguability, asthenia, headaches, and so forth, making them easy prey to intercurrent affections.

Treatment.—The treatment of these cases in any stage is, in the writer's experience, satisfactory. The great point to remember is the probable nature of the process of compensation which the organism is endeavoring to carry out. That would make one believe that suprarenal gland therapy is indicated throughout on account of the patent deficiency of this organ in these cases. And yet in our hands administration of suprarenal products is often disappointing. The whole gland perhaps has

given better results than epinephrin, although the latter, either hypodermically or (even against the dictum of the pharmacologist that it is inert when administered per os) by mouth in larger doses is good to tide over exceptionally bad days of fatigue and exhaustion. But the prime agent—the author believes almost a specific one—is pituitary gland in some one of its varied forms. Whole gland feeding in fairly large doses (2 to 3 grains t.i.d.) may be given in appropriate cases. But usually the dosage should be much smaller and given at greater intervals; one-half or one-quarter grain every second or third day has given success in several patients. Occasionally, pituitrin hypodermically 0.50 to 1.00 c.c. per day or alternate days for one or at most two weeks at a time is excellent as supplementing the feeding of pituitary gland. Occasionally, in cases with pronounced genital delay, anterior lobe pituitary gland gives fair results. In those cases with vagotonic symptoms, hyperacidity, and conditions resembling gastric ulcer, atropin in doses to physiologic tolerance is indicated, and gives results. But the pituitary feeding in itself alone produces highly satisfactory improvement in many cases. Under its use the headaches disappear, the fatiguability diminishes, the blood pressure and blood sugar content increase, and the case goes on to cure. Gradually the pituitary feeding can be diminished and finally discontinued. In the older cases, in which the sella persists in remaining small (T. R., Fig. 10, and J. S., Fig. 11), constant feeding would seem to be necessary; at all events, the patients relapse as soon as treatment is stopped. Indeed, the patients themselves reach that point of accuracy of judgment in feeding the gland to themselves that they can determine the size and frequency of the dosage necessary to maintain them comfortably.

Endocrin Disorders in Association with Muscular Dystrophies

Historical.—Early investigators of the progressive muscular dystrophies of the school of Charcot had at first placed them in the class with the atrophies and had thought the spinal cord to be the pathological focus of the disturbance. Then after several necropsies, especially one published by Lichtheim in 1878, of cases showing high-grade muscular atrophy in which no cord changes or peripheral nerve changes were demonstrable, opinion began to veer to the position that this second type was distinct from the one showing anterior horn changes in the spinal cord. This second group showed unmistakable evidence, in the muscular system itself, of disease; thus, the muscles show a large amount of fatty tissue between the muscle fibers. The muscle nuclei are increased in number and grouped together. There is splitting and vacuolization of the

muscle fibers and at times the muscle seems to have degenerated to a gray fatty mass. But more intensive and exhaustive examination further disclosed the fact that it was not only in the muscular system, but also in the bony skeleton and in the connective tissues and glandular elements that degenerative changes occurred. And as case after case was reported in full, it could be gradually seen, as though a curtain were gradually lifted, that more and more often, combined with the muscle dystrophy, there occurred concomitant disturbances indubitably dependent upon glandular dysfunction. Such were exophthalmic goiter, urticaria, hyperthyroidism, acromegaly, nyctalopia, prognathism, sexual infantilism, abnormal pigmentation, and so on. Keen observers, such as Erb, Marina and Jendrassik, had also noticed that in one case each of true progressive dystrophy that had come under their observation, a spontaneous cure had been brought about in the adolescent period, and each one had arrived at the same conclusions independently of the others, that the cures had resulted from a restoration of a disturbed balance in the internal secretory organs. Levi and Rothschild reported a case in 1907 which had made considerable progress under pituitary extract administration. Then in 1916, two important observations were made. The former by McCrudden and Sargent was the fact that progressive muscular dystrophy was accompanied by a hypoglycemia which accounted for the extreme fatiguability of the victims, and that glandular therapy consisting of combination of pituitary extract and epinephrin were of distinct value in the disease; and the latter by Timme, that the large majority of cases showed early calcification of the pineal gland and that borderline cases in which dystrophy was not the marked feature but fatiguability was the outstanding complaint, also showed these pineal shadows; furthermore, that pineal tumors gave rise to many of the symptoms seen in progressive muscular dystrophy. In 1917 Janney, Goodhart and Isaacson made metabolic studies of a number of cases of progressive muscular dystrophy and came to the conclusion that the changes demonstrated by them to exist were similar to those produced by dysfunction or removal of any one of several of the ductless glands, notably the thyroid, suprarenal or pituitary. Hence it seems that the time is ripe to include in any multiglandular study some reference to the syndromes presented by the muscular dystrophies and asthenias.

Classification.—*Types of Progressive Muscular Dystrophy.*—The classification adopted by Erb of the various types of this disease was accepted by Charcot and Marie, and is here reproduced as being sufficiently general to include all types that have been described.

1. Dystrophia muscularis progressiva (infantum).
   a. Hypertrophic form.
      (1) *With pseudohypertrophy.*
      (2) *With true hypertrophy.*

b. Atrophic form.

(1) *With primary facial involvement (Duchenne's infantile form).*

(2) *Without facial involvement. Simple atrophic form.*

2. Dystrophia muscularis progressiva juvenum et adultorum (juvenile form).

It is characteristic of the familial, hereditary forms to exhibit conditions at times of one of these groups, at others, of another group; so that in several generations of the same family individuals will be found to conform with almost any one of the types outlined above.

Types Manifesting Endocrinopathic Features.—We shall dwell chiefly upon those types of progressive muscular dystrophy that accent the endocrinopathic characteristics. Various authors have described atypical forms of muscular dystrophy, that is, they were atypical either in their course or their chronicity, or else in the groups of muscles affected or in the intensity of such impairment: in the presence or absence of contractures; in the slow or rapid involvement of the entire skeletal structure, together with the muscular, making of the patients helpless cripples, and ending in death in a comparatively short time. It will also be noticed that as we progress the recent authors show more and more marked a tendency to include symptoms referable to the sympathetic nervous system and the endocrin glands.

Barsickow's Group.—Barsickow's group is late in appearance, slowly progressive and not fatal. It was the first group of great importance, studied by Barsickow in 1871, and consisted of twenty-four cases occurring in two families from one ascendant through five generations. It is presented in extenso because of its importance. A composite picture of Barsickow's cases showed that the members of the widely scattered families in which they arose were as a rule in good health and lived to be old. The great grandfather had only a stiffness in gait and carriage, and yet twenty-three of his descendants (five out of seven of his immediate children) showed muscular disease, not only in function, but also in muscle volume. The members seem to have been attacked without rule, seemingly showing some predisposition in heredity. The children remained healthy if the parents were unaffected, and there were an equal number of males and females attacked. The cause of the original incidence, Barsickow states, was probably lead poisoning, for this original grandfather was a typesetter and had had many attacks of lead colic. In some cases chlorosis, cholera and varioloid acted as preceding agents conducing to the development of the trouble. The onset in seventeen of the cases was at the following ages: five between the ages of 10 and 20, seven between 20 and 30, and five later in life.

The condition was ushered in by almost simultaneous affection of both an upper and lower limb, or both upper and lower limbs. The serratus

anticus was among the first muscles to cause trouble. The most prominent symptom was the disturbed muscular function; in the mildest cases being stiffness and rapid exhaustion, going to absolute paralysis of single muscles, or entire groups in severe cases. The involvement was symmetrical. In most of the cases the diseased muscles gradually disappeared or atrophied, and hypertrophy was very rare. Frequently there was a lordosis with winged scapulæ, with protrusion of the shoulders or flattening of the chest. Fibrillary twitching was rare, being seen only once in fact. There was in the skin occasionally *loss of pigment or abnormal coloring.* Of the eleven subjects who died while under Barsickow's observation, one was over 80 years of age, four over 70 years, three over 60, one 58 and two 33. Hence the disease apparently did little to cut short their lives.

Taking up Barsickow's individual cases, those that showed symptoms seemingly not accounted for in the usual syndrome of dystrophia musculorum progressiva, we see in his Case 1 the complaint of *rheumatoid pains* in many parts of the body, *dirty brown pigmented skin,* and *patches of vitiligo.* Case 19 was that of a woman of 40 in whom the fingers and toes easily fell asleep and got *cold, white and waxy in the winter.*

Case 7 was that of a woman in whom the disease began at the *menopause.*

The reason I mention the above symptoms, which in the light of our present knowledge are referable to a disturbed autonomic nervous system with inclusion of the endocrin glands is that the theory of Remak, Schneevogt, Jaccoud, and Dumenil relative to the dependence of the affection on such disturbance of the vegetative system has now been shown to have some foundation.

The microscopic examination of the muscle fibers in Barsickow's cases showed changes in the muscle fibrils, some of which were much thickened, while between the primitive muscle bundles were many fat cells and connective tissue. The skin spots appeared in the neighborhood of recently affected muscles. In three cases with necropsy there was no abnormality of the nervous system demonstrable, and yet the author inclined to the idea that the disease is of a "vasomotor-trophic-nerve character." The Barsickow cases undoubtedly belong to the Erb juvenile and adult types.

Friedreich's Group.—In Friedreich's group of cases the disease was early in appearance, rapidly progressive, and fatal. Friedreich published the cases of four brothers whose mother was unaffected by the disease, but two of whose maternal uncles died of it in their 15th and 16th years. The brothers cited died at 5, 6, 12 and 16 years of age. Intellectually they were all well advanced. The affection began as weakness of the lumbar muscles, with constantly increasing difficulty in arising from a sitting posture. Muscular atrophy began in the muscles on each side of the spine at the same time. There then arose a difficulty in raising the arms to the shoulders on both sides. One of the victims died of suffocation from an

asthmatic bronchial attack. In this series of cases the rapidity of the course to a fatal termination is the characteristic feature. The necropsy showed, among other atrophies, that the pectorals were reduced to thin grayish-red, skin-like lamellæ, through which the ribs showed.

Gowers' Group.—In Gowers' group the disease was early in appearance, rapid in progress, and was fatal in adolescence. Gowers, in a clinical lecture in 1879, reported four brothers, aged 9, 10, 5 and 3 years, all affected, whose parents were both healthy, but whose maternal uncle died at 15 of a wasting disease. These patients had a little difficulty in putting their feet down on the floor on account of a tense, shortened Achilles tendon. The extensors of the knee and hip were weak, the flexors of the hip were feeble. The latissimus dorsi and the lower part of the pectorals were gone. There were no sensory changes, the knee-jerks were absent and there was a marked lordosis. The upper limbs were weak, although they moved freely. Gowers reports that out of 220 cases that he collected from the literature, 190 of the patients were males and thirty were females. While he mentions Barsickow's cases, yet he excludes them from his statistics, because they were all of the adult type. Some generalizations from these 220 cases are drawn by Gowers: (1) the disease is almost never heard of on the side of the father; (2) the age of onset is an etiologic factor of great importance and occurs in the worst cases before the 6th year; the more severe the case, the earlier it begins; (3) occasionally the disease follows physical injury; (4) shortening and permanent contractions of certain muscles lead to distortions in the positions of the joints; especially contraction of the calf muscles, leading to inability to place the heels on the floor; (5) the patients lose the power of standing at 10 or 12 years of age, and death supervenes between the 14th and 18th years; (6) of diagnostic importance is not the actual muscular enlargement, but the distribution of the muscular disease, especially the wasting of the lower pectorals and the latissimus dorsi; (7) the later the appearance of the disease, the more slowly it advances; the older the patient, the better the prognosis.

The commentary on these cases is that some of the conclusions, especially the last, are quite contrary to those reached in other types of the disease, to be described hereinafter.

Erb's Group.—Erb's types are of the accepted classification of progressive muscular dystrophy. In one of his publications Erb gives a general description of the juvenile type of the disease, saying that it begins always before the 20th year and usually with atrophy of the upper arms and shoulder girdle muscles and is often combined with hypertrophy. There are no reactions of degeneration and no muscular fibrillary twitching. The following muscles are almost constantly affected: pectorals (except the clavicular portion), cucullaris, latissimus dorsi, biceps and brachialis anticus and the long supinator. The glutei are weak and calves large.

The disease lasts from 20 to 40 years, with periods of quiescence. Erb states that this juvenile form is identical with Friedreich's hereditary progressive muscular atrophy. These latter forms belong in the same group with pseudohypertrophy.

In one publication, Erb gives the results of the examination of the available pathologic material of all these forms and says in summarizing that all the noticeable changes are in the muscle fiber chiefly, from an increase in volume to absolute disappearance of the muscle. There is an increase in the muscle nuclei and these are both normally and abnormally placed. There are clefts in the long axis of the muscle between the muscle fibers and an increase of connective tissue is found with a later deposit of fat cells and a thickening of the vessel walls. As a result of the identical pathologic findings in all forms of this elusive muscle disease, he proposes the classification of all these forms as types under the generic term of dystrophia musculorum progressiva. This classification has already been given earlier in this chapter.

Among other types the next cases of importance in the development of the semeiology of the disease were reported by Prager. Here the patients, two in number, were children of first cousins, who themselves were free of the disease. The importance of the citation of one of these cases is in the fact that while the patient, a woman of 48, had always had a waddling gait and a difficulty in going upstairs, yet after her first puerperium, which lasted three months, the difficulty in walking was so intensified that she needed support. Her muscular system gradually underwent the usual atrophies in the pectorals, latissimi, trapezius, rhomboids, biceps, deltoids, triceps, and supinator longus; but these atrophies were disguised by masses of fat in the arms and legs. To these physical signs, however, were appended the statements: (1) the patient was *easily excited and then developed a tremor;* (2) there was difficulty in deglutition for fifteen years; (3) *dyspnea in cold weather,* and (4) *increase in stools.* Further on is the remark that the patient had a *"struma" on the neck* and complained of *urticaria.* That is, she was a hyperthyroid subject. We shall find as we go along in the analysis of the symptoms as presented by the author frequent indications of disturbance in the endocrin system. In all probability, had such indications been then understood, there would have resulted a far wider range of symptoms in the muscular dystrophies; for what to the older observers probably appeared negligible in this regard, now assumes great importance. We shall see how more and more often in later years investigators have described conditions present in progressive muscular dystrophy, apart from the actual muscle changes, that are seemingly part of the disease process; which conditions have received but scant reference in the earlier works, presumably because they seemed so utterly adventitious. So Hahn states that *skeletal anomalies* are often seen and the idea is now that these are part of the condition of progressive muscular

dystrophy; and he cites Friedreich that bone atrophy is not secondarily due to disease of the bone through immobility of the joint, but to nervous and trophic influence. Eulenburg had a case which was *combined with acromegaly.* Hahn's conclusion is that because so many cases show bony changes, there may be some connection between them.

Bregman cites cases in which together with a "facies myopathique" there was difficulty in looking up and in closing the eyes; inequality of the pupils and of the palpebral fissures. This is interesting from the fact of the frequent involvement of the pineal gland; in which condition just such eye muscle difficulties arise (Bailey and Jelliffe). Bregman's cases further showed internal glandular disturbances as follows: In Case 1 the patient could not close the eyes properly and had *nyctalopia;* also there was *intense sweating* of the extremities with *cyanotic hands* and a *pulse of 100.* In Case 2 there was marked *prognathism, the upper teeth standing prominently forward;* the skin was *mottled like marble.* In Case 4 the hands and feet were *livid;* there was *large skeletal development of the hands and feet in contrast to the rest of the skeleton,* and marked *protrusion of the upper jaw.* In Case 5 there was extremely large body growth. In these cases there is manifestly disturbance of both pituitary and thyroid glands.

Cestan and Lejonne publish two cases with contractures and state that it is banal to say that contractures accompany all forms of progressive muscular dystrophy, but that ordinarily the contractures are slight and rarely sufficiently marked to alter the general attitude of the myopathic patient. Schultze presents two cases, both with necropsy, of brother and sister; in the former there was a thinning of the long bones, the humerus being thinner than the middle finger of a normal hand, and the medullary cavity very small. The sister had a stiffness in all the joints of the body, with atrophy of the bones. Schultze states that he had found only two other instances in the literature in which was found bone atrophy with muscular dystrophy, one a case of Friedreich's and the other Le Gendre's. In all these cases the atrophy was a concentric one of the long bones with no diminution in the length. In Le Gendre's case there was also an undue *hypertrophy of the genitals,* with an *enlarged prostate gland* in a youth aged 20; while Friedreich's case showed *infantilism in the sexual organs, voice* and *facial expression.* The necropsies in Schultze's cases showed no apparent changes in the spinal cord, not even in the ganglion cells, and he therefore concludes that we must look elsewhere than in the nervous system for the cause of this "riddle-like disease," and advises us that we cannot neglect the theory of predisposition, with accidental factors superimposed, such as overstrain, trauma, underfeeding, infection and intoxication.

O. With reported a familial type of the disease affecting three boys in one family and sparing the four girls. What interests us in these cases is the *involvement of the tonsils,* which were hypertrophied, a chronic

angina, a *hypertrophied lower jaw*, with difficulty in mastication and deglutition.

An article of extreme importance on account of the cure of the patient, by Marina, describes a case of a girl of 8½ years of age, who had all the signs of a beginning dystrophy with hypertrophic deltoids and gastrocnemii and such weakness in the shoulder girdle group that she could barely lift her arms horizontally. He lost sight of her for five years and then she appeared again entirely well. The author corresponded personally with Erb in this matter, questioning him as to whether a patient with muscular dystrophy had ever in his experience been cured, or whether he had ever seen "formes frustes" of this disease. Erb replied that he had never seen a single case of "forme fruste"—they had all been progressive—but that he had seen one single case of cure in a young English girl. Erb and Marina agreed that the cure in both of these cases was to be credited to the normal evolution of the patient; presumably to the fact that following the beginning of menstruation, normal development of the internal secretions succeeded, a most pregnant idea in the light of our present knowledge of the interrelation of the ovaries with the other endocrin glands. A fitting companion piece to the above is the case of Levi and Rothschild of a myopathic atrophy which showed considerable improvement on pituitary extract.

Henri Claude in 1908 described a case of familial progressive muscular dystrophy of rather different character from the usual in that the patient had asymmetrical atrophies, more marked on the right side. Besides the muscular condition, the bones on the right side were less developed than on the left, as shown by röntgenogram, and there were vasomotor changes particularly evident in the right hand, with perspiration and cyanosis. In cold weather the patient could not use this hand on account of the disability thereby occasioned. The temperature of the right hand was constantly lower than the left and the sphygmomanometric pressure was also less on the right side. Claude drew the conclusion from these findings that the whole disease picture does not embrace merely the muscular difficulty, but includes as well the central or peripheral nervous systems.

Jendrassik, after citing the cases of Marina and Erb, above mentioned, in which a seemingly spontaneous cure had been accomplished in muscular dystrophy coincident with adolescence, presents two somewhat similar cases, of which the one was a true progressive dystrophy. The patient was a girl who, just before puberty set in, had had the dystrophic process cease, and then after menstruation had been established became entirely cured, even to the return of the knee reflexes. There had been a precocious body growth between the 10th and 11th years, in which the breasts had participated, growing to a mature size.

Von Werdt describes a case with necropsy, which arose in a woman

at the advanced age of 46 and was not familial. It came on after a first pregnancy complicated with phlebitis. She became immediately bed-ridden, and remained so until her death at 63 years. The postmortem examination showed, besides the usual muscle condition, changes in the *thyroid,* which had developed a *large colloid struma* with but a little functionating tissue, and a small *tumor in the spleen, softened suprarenals, small pancreas,* somewhat *atrophic ovaries and small fatty deposits in the liver.* This case is interesting and suggestive as having developed after a disturbance of the *ovaries* due to a late first pregnancy.

Boveri described several members of a family afflicted with muscle dystrophy in which some of the muscles had been entirely replaced by fibrous tissue or fatty tissue, and thought it remarkable that *all of the patients had also exophthalmic goiter.* Collins and Climenko, among their numerous cases, make mention of the general growth anomalies in several, apart from the general muscular dystrophy. Thus, one patient had a *general adenitis* with *abnormal teeth,* especially the incisors, and *undescended testicles.* Another one had spongy gums, *poor and irregularly placed teeth,* a *high arched palate, long uvula with large tonsils;* at the age of 14 this patient was *undersized* and had as yet no signs of puberty.

Other authors report the presence of anomalies in the skull with asymmetry. Seegard in 1905, on the basis of twenty-one cases, disputed the hereditary factor in the etiology and claimed the entire process to be a metabolic one.

McCrudden and Sargent, in a careful laboratory study of a case of progressive muscular dystrophy, showed that a condition of hypoglycemia probably underlay the great muscular fatiguability. On account of the close relationship between *hypoglycemia, muscular asthenia* and *deficiency of the suprarenals and hypophysis,* epinephrin and pituitary extract were administered with resulting improvement in health, strength and weight.

In 1916 Timme (*a*) presented a series of 14 cases in one family occurring through three generations; six of the patients he had examined personally. The characteristics were the usual atrophy and hypertrophy, but the course in all was extremely benign. Timme stresses the point that five of the six showed pineal shadows in the röntgenogram, even though some of the affected members were only adolescents. He presents, in juxtaposition to the symptoms presented by these cases the characteristics of many patients known to have pineal tumors which had been confirmed by autopsy. The literature gives many such. There are many striking resemblances in the two groups. Timme concludes that too early pineal involution may be responsible for many of the symptoms of progressive muscular dystrophy. He cites cases also that give symptoms of fatiguability only of the dystrophy syndrome without apparent muscular disturbance, and in them he likewise finds pineal shadows. Evidently, according to his views, early

pineal involution plays an important rôle in the symptomatology of progressive muscular dystrophy. He confirms McCrudden and Sargent's findings of hypoglycemia. In 1917 Janney, Goodhart and Jacobson examined several cases of dystrophy and found, likewise, hypoglycemia and delayed glucose utilization. They also placed great stress upon the abnormal appearance of creatin in the urine with normal creatin in the blood. The creatin in the urine, they believe, is always abnormal, and in all probability is allied to the same causal factor that produces urinary creatin in myxedema, cretinism, dyspituitarism and Addison's disease—all endocrinopathies.

Fig. 12. Brothers both affected by progressive muscular dystrophy. Note hypertrophic calves and thighs, and atrophic shoulder girdle musculature. Older brother is more advanced in the disease—has more atrophy and greater lordosis. Note postures.

From several viewpoints, then, the dystrophies are rapidly coming to be regarded as endocrinopathies.

Onset, Symptomatology and General Course of the Disease.—Under the discussion of "Types of the Disease," practically all the necessary facts of onset and progress are included, hence only a general statement need be given here. The onset may be at any of the earlier periods of life in the far greater number of cases, although occasionally one is reported as occurring as late as the menopause. The mode of onset is usually insidious—a slight difficulty in arising from a sitting position—some extra exertion necessary to mount the stairs—an increasing disability to raise the arms above the head, are characteristic forerunners. From this initial disturbance, the progress varies. It may spread rapidly to various symmetrically disposed muscle groups, such as the shoulder girdle group, or the pelvic girdle group, with more or less rapid atrophy of the muscles involved. With the atrophy, contractures in various important tendons take place so that full extension becomes impossible. Thus, the hand and arm cannot be at the same time fully extended, the heel cannot be placed on the floor with the remainder of the foot, unless the knees are flexed. While atrophy of the affected muscles is the rule, other groups apparently hypertrophy. Especially is this true of the calves, which at times seem

Fig. 13. Method of arising in muscular dystrophy. "Climbing" up on his own framework, due to weakness of muscles of thigh, calf and back.

Fig. 14. Shows atrophy of shoulder girdle muscles, scalenes and especially pectorals. The pectorals show only a few bundles remaining.

enormous. But this hypertrophy is not commensurate with power. Indeed, their power diminishes quite, if not entirely, as rapidly as that of the atrophied muscles. For the hypertrophy is not a true increase of normally acting muscle fiber, but of interposed fatty bundles with degenerated muscle. At times the hypertrophy is entirely innocent of harboring any normally acting muscle tissue whatever, but is a mass of gray-looking, fatty consistency. Occasionally the subscapularis, or the infrascapulæ or the serrati appear hypertrophied. The increasing disability limits more and more the voluntary exercise of the body, the contractures

Fig. 15. Scoliosis in muscular dystrophy showing marked unilateral weakness of muscles of back.

become more and more pronounced, the atrophy is increasingly evident, and finally nothing but an apparent skeletal framework with little or no muscle covering, and in all positions of contraction, results. Lordosis arises early in the disease. Death ensues, either through intercurrent disease or through the increasing asthenia. There are all grades and combinations of atrophy and hypertrophy as there are all rates of progress in the disease, from one of intermittent remission with only gradually increasing disability so that ages of eighty years and over may be attained, to the fulminating cases lasting but two or three years, with rapid exhaustion. Various causes for the occurrence of the disease are given. Most investigators believe that heredity is a great factor, although Seegard, on the basis of twenty-one cases, denies this. Intelligent patients with the disease frequently give such causes as accident, emotional stress, acute

infection such as measles, scarlet fever, variola, exogenous toxins, such as lead—apart from hereditary factors. Possibly the matter lies as with tuberculosis, namely, that a predisposition exists which some efficient final cause may awaken. Apart from the muscle atrophies, dystrophies, and tendon contractures, many symptoms referable to the endocrin organs are presented. These are brought out under "Types of the Disease." There is an absence of signs referable to the spinal cord—which separates this group of disturbances from the spinal atrophies—such as fibrillary twitching; or in the domain of the sensory roots—such as pain or dysæsthesiæ of any kind. There are no sphincteric disturbances, at least until the final stages of the condition are reached. The reflexes, those that depend upon normally acting muscle response to nerve impulse, are deficient or absent in those joints served by atrophic or diseased muscle groups. The bony development in many of the cases shows distinct evidences of deficiency; the long bones especially, which upon röntgenographic examination are thin and slender but of normal length. The blood picture is usually negative as to the number and character of the cells, though the hemoglobin is frequently depressed. But the chemical examination is significant. The blood sugar content is low, well below 0.080 per cent. There is present in the urine an abnormal presence of creatin. Radioscopic examination of the skull frequently discloses a distinct pineal shadow, especially noteworthy in adolescents.

Fig. 16. Same patient as Fig. 15. Note dyspituitary features. Patient in condition of improvement due to glandular medication. At first completely bedridden with no ability to lift either arms or legs from bed level. Can now lift arms and sit up in chair.

Treatment.— Upon the basis of the recent findings of hypoglycemia, and a probable pineal disturbance, combinations of organotherapeutic agents have been used. These have for a basis the administration of pineal substance in increasingly large amounts over alternating periods of time, from a week to a month, together with pituitary whole gland and suprarenal whole gland feedings. The addition of a small amount of thyroid regularly, perhaps as low a quantity as one-fiftieth of a grain, accentuates the effect. Under combinations similar to those above given, the author has had some twenty cases of progressive muscular dystrophy under treatment. He has not as yet formally reported his results,

but up to the present writing, two cases seem to have gone to practical cure, two have markedly improved, three have remained stationary and of

Fig. 17. Same patient during glandular treatment. Can spontaneously lift arms and maintain them unsupported. Can lift knees from bed.

the remainder, all have retrogressed. The prognosis, therefore, as yet, must be unfavorable. Treatment apparently has helped in an occasional isolated instance, but cannot be said to be in any degree hopeful.

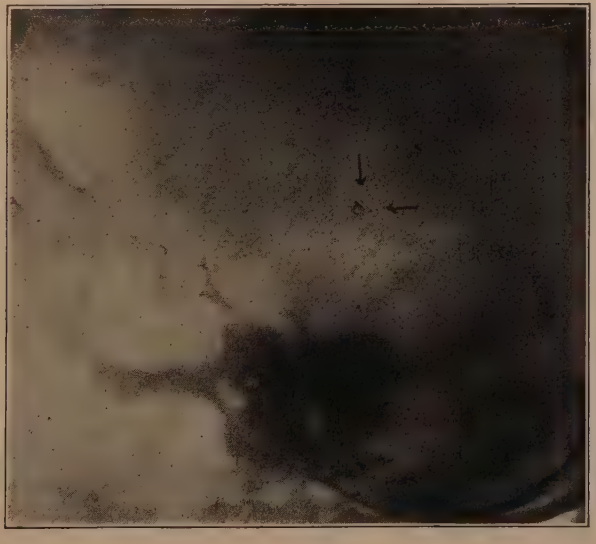


Fig. 18. Showing pineal shadow in the roentgenogram of the patient, Fig. 13 and 14.

Interrelation of the Endocrine Organs . . . . *R. G. Hoskins*

Thyroid—Relation Between Thyroid and Suprarenal Glands—Relation Between Thyroid and Hypophysis—Relation Between Thyroid and Gonads—Relation Between Thyroid and Thymus—Relation Between Thyroid and Pancreas—Relation Between Thyroid and Parathyroid Glands—Hypophysis—Relation Between Hypophysis and Thyroid—Relation Between Hypophysis and Gonads—Relation Between Thymus and Gonads—Other Relationships.

Interrelation of the Endocrin Organs

R. G. HOSKINS

COLUMBUS

That the various structures making up the endocrin system stand in intimate functional relations with each other has become a medical truism. The evidence that the hormone from one of the congeries influences others is in some cases fairly convincing. In other cases, however, the theory that such interrelationship exists stands upon a very insecure basis. The data bearing upon the subject are scattered through a wide range of publications, clinical, pathological and physiological, and they are often presented under misleading captions. Anything like an exhaustive compilation of the evidence is therefore practically out of the question. Much of the evidence, and especially that from clinical sources, moreover, is far from convincing, often consisting as it does of no more than the observation of concomitant changes in two or more endocrin organs. To what extent the simultaneous appearance of different endocrin anomalies indicates a definite relationship between the glands in question and to what extent it is merely coincidental or the result of some antecedent factor manifesting its influence in both, it is frequently, or indeed usually, impossible to determine. A major difficulty in the determination of interrelations among the various endocrin organs arises from the fact that precise knowledge of the functions of the individual organs is for the most part lacking.

Thyroid

The evidence of relationships between the thyroid gland and other endocrin structures is more extensive and better established than in case of any of the other organs of internal secretion. The thyroid will be discussed in relation to the suprarenal glands, the hypophysis, the thymus, the pancreas, the parathyroids, the ovaries, and the testes.

Relation between Thyroid and Suprarenal Glands.—Several observers have noted an augmentation of the volume of the suprarenal glands following the administration of thyroid material to experimental animals. R. G. Hoskins (*a*), in 1910, fed young guinea-pigs small quantities (5 to 15 mg.) of desiccated thyroid, from birth to the end of 15 days. At the end of this period the animals were killed and the suprarenals weighed. Those of the thyroid-fed subjects averaged 25 per cent heavier than those of the normal controls.

Iscovesco (1913) prepared an ether soluble material from the thyroid gland and administered it hypodermatically to rabbits. This resulted in a considerable degree of hypertrophy of the suprarenals.

E. R. Hoskins (1916) made a careful study of the effects of feeding thyroid material to albino rats. He observed that the suprarenals were considerably larger in the experimental than in the control series. In the younger females the augmentation amounted to 14.5 per cent, and in the older females to 16.1 per cent. In case of the males, the augmentation was 36.4 and 38.1 per cent, respectively, in the younger and the older subjects.

Herring (*c*) (1917), who employed larger doses of the gland material than did Hoskins, obtained more marked hypertrophy of the suprarenals. The average augmentation of weight in the females was 56 per cent and in the males 41 per cent. Herring noted that the cortex was chiefly affected, though the medulla also seemed to be influenced, as shown by the greater depth and extent of staining of the chromaphil material.

Hewitt (1920) has confirmed the results of the previous investigators mentioned. The additional observation was made that in the young rat, after the thyroid feeding was discontinued, there was a tendency for the suprarenals to regain their normal weight.

Kuriyama (1918), on the other hand, failed to observe any significant hypertrophy of the suprarenals after thyroid feeding, either with large doses for a short time or small doses over a longer period. No difference in the epinephrin content of the glands could be detected. Herring (*e*) (1920) suggests that these experiments, however, were unsatisfactory in that the investigator employed desiccated thyroid of unknown activity in doses which would be toxic if fully active. His animals differed markedly in ages and weights and the males and females were grouped together. It is quite possible, too, that the dietary factor played a part, since his animals received only dog biscuit and lard paste, and hence probably suffered from vitamine deficiency, a condition which, as McCarrison and others have recently shown, results in abnormalities of the suprarenals.

R. G. Hoskins, in 1910, reported some experiments upon guinea-pigs which might be interpreted as indicating suprarenal stimulation by thyroid feeding. To 28 pregnant females commercial desiccated thyroid was fed in small doses. This resulted, in most cases, in abortion or intra-

uterine death of the fetuses; 21 offspring, however, were secured. The weight of their suprarenals averaged 53 per cent less than that of normal animals of the same age. This depression was tentatively ascribed to flooding of the fetal circulation with an excess of suprarenal products due to stimulation of the suprarenal glands of the mothers. The interpretation is, of course, open to question.

The effect of experimental thyroid deficiency has also been studied by a number of investigators. Hofmeister, in 1894, performed thyroidectomy upon many young rabbits and studied the results in various organs. No significant difference between the suprarenals of the experimental and normal animals was established. Definitely negative results were also obtained by Bensen (1902). Most investigators, however, who have studied the results of thyroidectomy have devoted little attention to the suprarenals. Gley and Quinquaud (1914) reported marked increase in the relative weight of the suprarenals of rabbits after thyroparathyroidectomy. This increase was interpreted, however, as indicating not hyperfunction but degeneration. Tatum (1913) removed the thyroid from young rabbits 2 to 3 weeks old, leaving the inferior parathyroids intact. The operation resulted in hyperplasia of the suprarenal medulla and augmentation of the lipoid material in the cortex. Carlson has stated that "After complete thyroidectomy we invariably get a hypertrophy of the suprarenals to two or three times their normal size." Herring (*b*) (1916), on the other hand, in the case of 5 thyroidectomized rabbits, failed to obtain any significant effect upon either the weight or the epinephrin content of the suprarenals. Stewart and Rogoff (1921) have reported that the average weight of the suprarenals of 25 thyroparathyroidectomized rabbits was considerably greater than normal, and that the enlarged glands contained proportionately as much epinephrin per unit weight as those of normal animals. For a more detailed discussion of the evidence along these lines Herring's paper of 1920 may be consulted.

So far as the writer is aware, the study of clinical cases of thyroid disorders has not contributed any significant data on the thyroid-suprarenal relationship.

In view of the fact that the suprarenals are known to hypertrophy from a variety of causes, such as pregnancy, prolonged muscular exercise, avitaminosis, and perhaps intoxication of various sorts, the interpretation of the foregoing data is difficult. The weight of the evidence, although by no means conclusive, seems to indicate that the thyroid stimulates the suprarenals. The problem is worthy of further investigation, using a variety of species of animals.

Relation between Thyroid and Hypophysis.—The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the endocrin interrelationships. The experimental evidence is somewhat extensive and is fairly well supported

by clinical observations. Rogowitsch (1889) first noted that after thyroidectomy hypertrophy takes place in the hypophysis. In explanation of this condition, he propounded the theory that, in case of need, the hypophysis can assume, in greater or less degree, the thyroid function. Stieda (1890) repeated Rogowitsch's experiments upon 7 rabbits. He described the hypophyseal hypertrophy that resulted as due to an increase in the number of "chromophobe" cells of the anterior lobe with a vacuolization of their protoplasm. The chromaphil cells were not demonstrably affected, and there was no evidence of increased colloid formation. Tizzoni and Sentanni (quoted by Delille) performed thyroidectomies upon 2 dogs and noted 1½ and 4 years respectively after the operation results similar to those of Rogowitsch, except that there was a marked diminution of chromophobe cells. Gley (*a*) (1892), Leonhardt (1897), and Hofmeister (1892) obtained similar hypertrophy with rabbits, as did Alquier (1907) in the dog, and Thaon (1907) in the ram. Confirmatory results have been reported by Horsley, v. Eiselsberg, and Lusenna. Cimoroni (1907) studied the effects of thyroidectomy in the hypophyses of dogs and rabbits. He noted, not only gross hypertrophy, but also cytological changes which he regarded as evidence of enhanced secretory activity. Herring (*a*) (1908) failed to confirm the observations of these different investigators that the anterior lobe hypertrophies following thyroidectomy, but he did note evidence of increased activity in the pars intermedia. Hoskins and Morris (1917) found no changes in the hypophysis of frog larvæ following thyroidectomy. Rogers (1918), and later Hoskins and Hoskins (*d*), however, obtained positive results. The anterior lobe of the hypophysis reached a larger size, in proportion to body-length, in thyroidectomized than in normal tadpoles, as well as young, sexually mature frogs. More recently, the effects of thyroidectomy in puppies and young dogs have been restudied by Kamo. When the animals were sacrificed 1½ to 5 months after the operation, marked hypertrophy of the hypophysis, even to more than twice the normal size, was noted. The anterior lobe chiefly was affected. Trautman (1916) made an extensive study of the effects of thyroidectomy on the hypophysis of 30 goats. He noted marked alterations in all three parts of the gland, but regarded them as mainly of a degenerative type. His report includes an extensive summary of the literature.

Various clinical observers, for example Sharp (1916) and Mott (1917), have observed signs of overactivity in the hypophysis in conditions of spontaneous thyroid deficiency.

The evidence, on the whole, indicates rather definitely that thyroid deficiency leads to hypertrophy and secretory activity upon the part of the hypophysis. There is some disagreement, however, among observers as to the degree to which different portions of the hypophysis are affected.

The effects of experimental hyperthyroidism upon the hypophysis have been much less extensively investigated than have the effects of

thyroidectomy. Guerini (1905) noted hypertrophy, but since he obtained a similar result from the administration of pilocarpin and other poisons, he regarded it as merely a reaction to the thyroid as a toxin. Delille (1909) stated that in rabbits treated with thyroid material the hypophysis showed at first a slight hyperplasia, but soon reached a state of exhaustion. E. R. Hoskins (1916) observed some evidence of hypertrophy in the hypophysis of male rats to which thyroid was administered, but the female animals showed decrease of hypophyseal weight.

There is thus fairly convincing evidence of a definite relationship between the thyroid and the hypophysis. If Guerini's explanation of the effect of hyperthyroidism upon the hypophysis is accepted, the recorded observations support fairly well the theory of Rogowitsch that the organ can function vicariously for the thyroid. The evidence, however, does not exclude the possibility that the thyroid normally exercises an inhibitory influence upon the hypophysis, and that the hypertrophy noted in the hypothyroidism is due simply to the removal of this check upon its activity. That the administration of hypophyseal material can in a measure compensate for the loss of the thyroid is indicated by the results of Livingston (*a*) (1914) and Larson (1919). The latter observer studied somewhat extensively the effect of the administration of anterior lobe substance upon the development of thyroidectomized rats. The hypothyroid symptoms were ameliorated and life was definitely prolonged. Hoskins and Hoskins (1920) further noted that thyroidectomized tadpoles, which normally persist for months in the immature stage, can be made to metamorphose promptly by the administration of hypophyseal substance.

Relation between Thyroid and Gonads.—Clinicians have long held that the thyroid exerts an important influence upon the sex-glands. In cases of Graves' disease, the sex functions are often affected. Many observers have mentioned menstrual disturbances occurring during the course of that malady. The literature was discussed extensively by Sattler in 1909. He cited the observations of several other clinicians as to menstrual conditions in Graves' disease. In Trousseau's experience, all cases showed anomalies. Griffith observed amenorrhea in 6 of 28 cases. Many of West's 38 cases showed irregularity. In 48 cases reported by Russell, however, menstruation was regular in most instances. In Murray's 170 cases, 45 showed irregularities and 24 amenorrhea. In 19 of Manheim's 36 cases this function was normal. Many of Kocher's cases showed irregularities. Moebius, on the other hand, thought that menstrual disturbances are no more frequent in Graves' disease than in any other equally serious illness, while Oppenheim regarded amenorrhea as unusual. Rogers (1910) has reported that in his experience menstrual disturbances, with enlarged and tender ovaries, always occur in this disease. While such observations are by no means unequivocal, they indicate that menstrual disturbances are at least not infrequent. Rather more

significant is the fact that decreased libido and potentia coeundi, and even actual atrophy of the gonads, often occurs in this malady. A great many instances of this are on record. A summary and discussion of the literature may be found in Sattler's monograph, as well as the various text-books.

That hypothyroidism, either clinical or experimental, results in sex depression that may be so pronounced as to amount to complete impotence is well known. Gandy (1906), for example, described two clinical cases that illustrate the relation of the thyroid to the sex function very convincingly. His two patients, men of 25 and 33 years respectively, after having attained a normal adult sexual condition, developed myxedema. This was followed by reversion to a sexually infantile condition, indicated by atrophy of the genitalia and impotence. Many other similar cases are on record. Simonton (1919) has made the interesting observation that practically half the female and some of the male population of the Cumberland Valley, Pennsylvania, suffer from goiter. Most cases show definite hypothyroid symptoms. These are accompanied by scanty, irregular menstruation in the females and subnormal genital development in both sexes. In Simonton's cases, as in those of many other observers, the administration of thyroid preparations has materially ameliorated the symptoms of gonad depression.

In experimental investigations, thyroidectomy has resulted, at the hands of various observers, in a depression of the sex function with atrophy or degeneration of the gonads. Such findings have been reported by Hofmeister in the case of young rabbits, and by Lanz in goats. Lanz reported also the case of a man in whom surgical thyroidectomy resulted in a cretinoid state. The testes became markedly atrophic. Ceni noted a decided decrease in the production of eggs after thyroidectomy in hens. Alquier and Theureny observed a marked depression of activity in the testes after thyroidectomy in dogs.

So well established is the idea that thyroid deficiency results in sexual depression, that observers who have made thyroidectomies of recent years have usually not considered it worth while to report specifically upon sexual activities. Whether, however, the thyroid exercises an influence directly upon the sex glands is not so clear. Any process which retards general metabolism is likely to result in sex depression; and similarly, any general bodily stimulant is likely to result in augmented sex activity. It is quite possible, therefore, that the sexual manifestation in various thyroid perturbations are merely conditioned by the general metabolic reactions. In any case, however, the end result is the same, whether the effect be mediated directly or indirectly.

Relation between Thyroid and Thymus.—That the thymus is often enlarged in cases of Graves' disease is well known. Apparently this was first noted by Cooper in 1872. Capelle (1908) attempted to analyze the

literature as regards the frequency with which thymus hypertrophy occurs in thyroid disorders. He was able to collect 60 cases of Graves' disease in which autopsy records were available. Of the cases in which the patients had died of an intercurrent affection, thymus hypertrophy was noted in 44 per cent; of those dying directly of the disease, 82 per cent showed hypertrophy; and of those succumbing to operation, 95 per cent showed hypertrophy. Pappenheimer (1910), from a histological study of the thymus glands of three patients having Graves' disease associated with general status lymphaticus, reached the conclusion that the thymus showed "renewal of growth" rather than mere persistence. Although an enlarged thymus in Graves' disease is common, it is by no means always found (Hilderbrand, 1918; Blackford, 1919).

Thymus hypertrophy may be associated with simple congenital goiter. In Switzerland, where the disease is endemic, the offspring of goitrous mothers often show enlargement of both the thymus and the thyroid gland (Birnbaum). Marine and Lenhart have also noted enlarged thymus in young animals showing spontaneous thyroid hyperplasia. Whether the simultaneous occurrence of hypertrophy in the two organs is simply a reaction to a common cause, or whether hypertrophy of one conditions that of the other, cannot from such observations be determined.

That there is an element of true hypothyroidism in Graves' disease is believed by Anders, Janney, and others. Congenital goiter rather definitely signifies hypothyroidism. From the foregoing observations one might conclude that the thymus possibly in a measure assumes the thyroid function when the latter is deficient. That supposition receives some report from the observations of Dustin and Zunz (1918). These observers made a study of the weights of the thymus and thyroid glands in normal men killed in the war. They found in general that if the weight of the thyroid was small that of the thymus tended to be large, and vice versa.

The relation of the thyroid to the thymus has apparently received relatively little attention at the hands of experimental investigators. R. G. Hoskins observed that the offspring of female guinea-pigs to which thyroid substance had been administered had larger thymus glands than normal. Such an observation, however, is difficult to interpret. Gley (1894) studied the condition of the thymus gland in cases of a few dogs and rabbits from which the thyroid had been removed. Thymic atrophy was noted. Similar results were obtained by Cadéac and Guinard in the case of two lambs. Hofmeister, from a much more extensive series of thyroidectomy experiments in young rabbits, obtained negative results. Jeandelize, Lucien, and Parisot (1909), in 7 young rabbits from which the thyroid had been removed, noted in every instance diminution of the thymus weight. Worms and Pigache (1909) obtained somewhat similar results. In their animals the thymus glands, a few days after thyroidec-

tomy, were found to be degenerated, the parenchyma being largely replaced by connective tissue. In view of the fact that the thymus is particularly liable to atrophy in any condition involving malnutrition, it is impossible to determine from such observations whether the thyroidectomy as such conditions depression of thymus weight, or whether this latter represents merely one phase of impaired nutrition. E. R. and M. M. Hoskins (1919) noted in a large series of thyroidectomized tadpoles that the thymus gland persists and becomes relatively large. Since such tadpoles grow rapidly and ultimately become two or three times as large as the controls, it is possible to ascribe the thymus enlargement merely to the nutritional factor.

From the available evidence, no final decision can be drawn as to the existence of a definite relationship between the thyroid and thymus glands. That the two may be simultaneously affected under various conditions is fairly well demonstrated, but whether either plays a causal rôle in the changes of the other is unknown.

Relation between Thyroid and Pancreas.—That the thyroid has some relation to carbohydrate metabolism, and that the pancreas has an intimate relation with it, is well known. A decade ago much was heard of Falta's theory that the suprarenals, the pancreas, and the thyroid stand in a close triangular relationship. It was assumed, upon quite inadequate grounds, that the thyroid facilitates the mobilization of dextrose by exercising an inhibitory influence upon the pancreas. Later observations by Underhill and Hilldítch (1909) and others, however, have failed to bear out Falta's theory. McCurdy (1909) and others have shown that thyroidectomy raises the assimilation limit for dextrose.

Falta (1909) reported that in a single case, after thyroidectomy, an undoubted hypertrophy of the islands of Langerhans was found. Kojima (1916) and Hoshimoto (1920) have found that thyroid feeding results in hypertrophy of the pancreas.

In view of the highly complicated physiology of carbohydrate metabolism and of the profound effect which the thyroid has upon metabolism in general, no conclusion is justified from data now available as to whether the thyroid gland has any direct influence upon the pancreas as an endocrin organ.

Relation between Thyroid and Parathyroid Glands.—In his earlier studies on the parathyroid glands, Gley noted, following the removal of the thyroid and the internal parathyroid glands, the external parathyroids hypertrophied and assumed an appearance somewhat similar to that of the thyroid. He concluded, therefore, that under such circumstances the parathyroid may assume the thyroid functions. Later, however, after further experimentation he discarded this view. Vincent and Jolly (1905) also found, on microscopical examination of the parathyroids left behind after the removal of the thyroid gland, an appearance simulating that of the latter gland. Similar results were obtained by Halpenny and Thompson

(1909) in the dog, and Halpenny later noted a somewhat doubtful instance occurring in a rabbit. That the parathyroids undergo hypertrophy under such circumstances has been confirmed by several subsequent investigators. Most physiologists, however, have failed to see in this satisfactory evidence that the parathyroids assume any thyroid function, although this view was vigorously maintained by Vincent for several years. More recently, Vincent and Arnason (1920) have expressed doubt of the validity of Vincent's former position. The consensus of opinion at the present time is that the thyroid and parathyroid glands are independent in function. Whether either influences the activity of the other is unknown.

Hypophysis

Relation between Hypophysis and Thyroid.—Hallion and Alquier (1908) fed to 5 rabbits for a prolonged period extracts of the whole hypophysis of cattle. At autopsy the thyroid glands were found to have less than the normal amount of colloid and the cells were somewhat more columnar than normal, i. e., the glands approached the hyperplastic type. Rénon and Delille (1908) obtained similar results from intraperitoneal injections of hypophyseal extracts. They found that posterior lobe extracts had much the same effect as whole gland extracts. Lucien and Parisot (1909) repeated the experiments of Rénon and Delille but obtained somewhat different results. The thyroids in their animals were from 10 to 40 per cent heavier than those of the controls and had an increased amount of colloid, an appearance "hardly indicating increased activity but rather resembling a simple goiter." Sandri (1909) obtained negative results in guinea-pigs both from feeding and from injecting hypophyseal extracts. The writer (1911) obtained similar negative results in case of 19 young guinea-pigs. More recently Pardi (1916) has confirmed the results of earlier observers to the effect that hypophyseal extracts in rabbits cause an augmentation of the colloid in the hypophysis. Hofstätter (1919) treated 70 rabbits by intramuscular injections of "pituitin," 1 c.c. every two days, from 20 to 80 days. He noted a decrease in the colloid of the thyroid gland. The use of this extract is not equivalent, however, to that of the whole gland.

Several authors have studied the effect of extirpation of the hypophysis upon the thyroid. Smith (1916) and Allen (1916) independently discovered that hypophysectomy in tadpoles results in marked diminution in the size of the thyroid gland. Cushing (1912) reported exactly the opposite result in case of 6 dogs, whereas Bell in this animal obtained negative results. Houssay (1916) reported that in the dog extirpation of the hypophysis resulted in an excessive accumulation of colloid and sometimes degeneration of the cells.

The clinical literature throws little light upon the problem under discussion. Simultaneous disturbances in the hypophysis and the thyroid have been reported by various observers, but under conditions which render impossible the determination as to which condition was antecedent. Exner (1909) reported two clinical cases, however, which were rather clean-cut. In both instances the hypophysis was extirpated for the relief of acromegaly and later there was found among other results an undoubted hypertrophy of the thyroid gland. Whether this indicated an accumulation of colloid signifying depressed thyroid activity or hyperplasia of the gland cannot be determined.

The evidence as a whole does not permit any definite conclusion as to the effect of the hypophysis upon the thyroid. The problem demands further study in a variety of animals.

Relation between Hypophysis and Gonads.—Clinicians have long believed that an intimate relationship subsists between the hypophysis and the sex glands. Cessation of menstruation in the female and impotence in the male are well-recognized initial symptoms of acromegaly. In Exner's two cases, mentioned in a preceding paragraph, the onset of the disease was soon followed by amenorrhea. The restoration of menstruation after removal of the hypophyseal tumors would seem to indicate some sort of specific causal relationship. Von Eiselsberg (1907) reported the case of a man 20 years old, who developed a typical case of dystrophia adiposogenitalis with hypophyseal tumor. The tumor was successfully removed and a year later marked genital development had occurred. The clinical evidence is discussed at length in the chapters on the hypophysis.

The earlier experimental investigators obtained negative results from feeding or injecting hypophyseal extracts (Hallion and Alquier, Rénon and Delille, Sandri). Of later observers E. R. Hoskins (1916), Frank (1919) and Sisson and Broyles (1921) using rats as the experimental animals have also obtained negative results. Goetsch (1916), on the other hand, from a small series of rats reached the conclusion that hypophyseal feeding results in a marked stimulation of the sex glands. These results are discussed at length in the chapter on the Physiology and Experimental Pathology of the Hypophysis. Marinus (1919), in a larger series (about 30) noted increased growth and more rapid development of the reproductive system, as well as earlier production of young when rats were fed with anterior lobe substance. Pars tuberalis material, on the other hand, gave negative results. The writer, in collaboration with F. H. Allen, in experiments on the white rat not yet completed, has obtained some evidence that hypophysis feeding results in earlier reproduction. The variability of preparations fed may explain the discrepancy in various cases.

Clark (1915) reported that feeding hypophyseal substance to fowls resulted in increased egg production. Winternitz (1916) confirmed this

result in one group of 11 chickens, but subsequently obtained negative results in two other series of experiments. Simpson (1920) also obtained completely negative results.

It is thus seen that the trend of the evidence indicates, though by no means conclusively, that the administration of hypophyseal substance causes some degree of stimulation of the gonads. There is available some clinical evidence also tending toward the same conclusion. Stelwagen (1916) reported the cure or amelioration of several cases of impotence in the male from pituitary medication. In view of the marked effect which mere suggestion may have in such cases, however, little stress can be placed upon these observations. Goetsch (1917) mentioned several clinical cases in which such conditions as irregular menstruation, amenorrhea and sterility were greatly benefited by the use of hypophyseal extracts. The restoration of menstruation, following the use of pituitary extract, after 12 years of amenorrhea, was reported by Jona (1916). In other cases, however, the use of hypophyseal substance has had the effect of depressing menstruation. A case was reported by Ebaugh and Hoskins (1921) in which hypophyseal combined with thyroid and suprarenal feeding seemed to bring about testicular development in a boy of 16 with marked infantilism.

In addition to the clinical evidence of infantilism associated with disorders of the hypophysis, there is available experimental evidence that hypophyseal deficiency results in a depression of the sex functions. Cushing (1912) has cited some instances of this. Bell, in his monograph, also supplies evidence along the same line. Houssay (1916) had the problem under investigation for several years. He found that in young dogs that survived the operation genital arrest or retardation was characteristic. In adults testicular atrophy occurred in all cases in which there was ablation or extensive lesion of the whole gland or of the anterior lobe alone. Doubt has recently been cast upon the adequacy of such data, however, by Camus and Roussy (1920). These investigators have found it possible to produce well-marked genital infantilism in experimental animals merely by injuring the tissues at the base of the brain near the hypophysis, but leaving that organ intact. The whole problem of the relation of the hypophysis to the sex organs is obviously in need of further investigation.

The effect of castration upon the hypophysis has been studied by a number of investigators. Cecca (1904) briefly reported negative results in both sexes. Fichera (*a*) (1905) studied the matter somewhat extensively in 65 animals, cocks, buffalo, cattle, guinea-pigs, and rabbits. He observed well-marked hypertrophy of the anterior lobe of the hypophysis, together with a hyperplasia of the eosinophil cells. In 3 capons he found that injections of testicular extracts caused a rapid disappearance of the eosinophilic substance. Fichera's results seemed well established and

were widely accepted as valid. His findings have been confirmed by Tandler and Grosz (*a*), by Soli, by Cimorini, and by Schutz (cited by Cushing, 1910) on animals, and somewhat doubtfully by Kon (1909) in a study of the hypophyses of 7 women and 1 man after surgical castration. Marrassini and Luciani (1911) reported a somewhat elaborate study of the problem. Their observations were made on sheep, cattle, dogs, rabbits, guinea-pigs, and domestic fowls. They were unable to detect any significant difference between the hypophyses of the normal and the control animals. Similar negative results were reported by Livingston (*c*) (1916). Rabbits served as experimental animals. From an extensive body of data he reached the conclusion that neither males nor females show a constant hypertrophy of the hypophysis following extirpation of the gonads. Massaglia (1920) found in 4 capons hypophyses approximately twice as large as those of 7 normal control cocks.

The weight of the available evidence indicates that castration results in some degree of hypertrophy of the hypophysis. There is some evidence that the eosinophilic cells are especially affected. The problem, however, cannot be regarded in any way as settled.

Relation between Thymus and Gonads.—In view of the fact that a certain degree of involution of the thymus gland occurs at about the time of puberty, a theory has gained considerable credence that an important relationship subsists between this organ and the gonads. Apparently the first to investigate the matter experimentally was Calzolari (1898). In each of 6 rabbits previously castrated he found the thymus was larger than in normal animals. Henderson (1904) compared the weight of the thymus gland in 100 castrated male cattle with the normal weight for this species, and found evidence of persistence of the thymus. Similar observations were made in guinea-pigs and rabbits. Henderson stated also that in cattle of both sexes that had exercised the reproductive function, thymus involution was accelerated. Goodall (1905) made a histological study of the thymus glands of guinea-pigs previously castrated and noted that both the lymphoid tissue and the corpuscles of Hassall shared in the delayed atrophy which he regarded as characteristic. Soli, in 10 rabbits and 15 capons, noted thymus persistence after castration, and Tandler and Grosz made similar observations in roebucks, dogs, and goats. All such observations are subject to the general criticism that castration tends to result in overgrowth or a high state of nutrition in various tissues. It is quite probable, therefore, that these observers have noted merely the converse of the thymus wasting which occurs in inanition or emaciation from any cause.

Several observers have studied the effects of thymectomy on the sex glands. Paton (*a*) (*b*) (1904, 1911) reported that this operation causes a more rapid growth of the testes than normal. Soli, however, reported precisely the opposite effect. Bracci (1905) was able to detect no gross

or microscopic changes in the gonads of thymectomized rabbits. Lucien and Parisot (1909) found the weight of the testes of 2 thymectomized rabbits below that of their normal controls. The ovaries of 3 other rabbits, however, were slightly larger than the controls. Magnini (1912) obtained negative results in rats, as did also Pappenheimer (1914). More recently Park and McClure (1919) have made an extensive investigation of the effects of thymectomy in dogs. They were able to detect no significant difference in the gonads of the experimental and control animals. On the whole there is little substantial evidence to indicate that the thymus exercises any significant influence on the sex glands.

Other Relationships

That there is a relationship between the pineal gland and the gonads, and between the suprarenal cortex and the gonads, is indicated by a considerable number of data. The evidence will be found in the chapters on Physiology and Experimental Pathology of the Pineal and of the Suprarenal Glands respectively.

Many other interrelationships than those herein discussed have been postulated. In the opinion of the writer, however, there is not enough definite evidence to render the matter worthy of formal discussion in a work of this sort. The literature up to 1910 has been reviewed by Hoskins (*c*) (1911). The literature since 1916 has been largely abstracted in Endocrinology.

Whether, as is often assumed, all the various endocrin organs stand in intimate functional relationship with each other, has by no means been demonstrated. The facile theorizing that has been indulged in by numerous uncritical writers is not justified. A diagnosis of "pluriglandular dystrophy" or "pluriglandular syndrome" is often merely camouflage for ignorance. A great many more careful investigations are needed. The problem is one of the most difficult in all biology. In its solution the demands of adequate technique, extensive data and rigid logic are unescapable. These demands in the past have been largely ignored.

SECTION XVI

The Importance of Endocrinology for the General Practitioner . . . . . *Charles E. de M. Sajous*

Introduction—The Major Endocrine Syndromes—Addison's Disease and Other Hypoadrenias—Exophthalmic Goiter—Myxedema—Gigantism and Acromegaly—Dystrophia Adiposogenitalis—Tetany—Status Thymicolymphaticus—Diabetes Mellitus—Hypogenitalism (Eunuchism; Eunuchoidism; Menopause)—Hypergenitalism (Pseudohermaphroditism; Premature Puberty; Hirsutism)—The Multiglandular Endocrine Syndromes—The Significance of Balanced Activities of the Endocrine Gland for Normal Structure and Function—Special Opportunities for Observations by General Practitioners—The Value and Place of Hypothesis in Endocrinology—Use of Endocrine Products in Therapy—The General Practitioner and the Future of Endocrinology.

The Importance of Endocrinology for the General Practitioner

CHARLES E. DE M. SAJOUS

PHILADELPHIA.

1. Introduction

Swale Vincent, writing in 1913, said "Sajous apparently postulates a relationship between all the ductless glands whose functions, according to this writer, dominate most of the bodily activities, normal and pathological." This comment referred to the author's treatise published in 1903 in which an effort was made to describe the great significance of the internal secretions in physiology, general pathology and the clinic. Since that work was published there has been a growing recognition of the relationship of the glands of internal secretion to all the bodily and mental functions. One sees this in evidence throughout the whole realm of medical thought. It is, of course, naturally gratifying that time has sustained the position taken by the writer some twenty years ago.

Work upon the endocrin glands, their structures, their functions and their pathology has led to great advances in knowledge during the past two decades. Anatomists, physiologists, biochemists, pharmacologists, pathologists and, above all, clinicians have contributed to these advances. Monograph after monograph has appeared in every country of the world in which active medical research is carried on. Articles upon endocrinological subjects now appear in all the medical journals, not only in the general but also in the special journals. Recently, in this country, a journal devoted entirely to the subject of endocrinology and containing both original papers and abstracts of the work done throughout the world upon endocrin subjects has been started. Medical clubs have, I am glad to say, been formed in the United States for the study of endocrin subjects and the Association for the Study of Internal Secretions, which was organized a few years ago, now has a large membership drawn not only from every State in the Union but also from foreign countries. Thus, the subject of endocrinology, which was once looked upon somewhat askance, has of late years become one of the most important fields of medical research.

The general practitioner has a keen sense of practical values. It

is not surprising, therefore, that the man in everyday practice early became interested in the internal secretions and strove to value the growing knowledge of the subject for diagnosis and therapy. That he should have made some mistakes is not at all to his discredit. Mistakes are inevitable in the early application of scientific discoveries to practical medicine. The important thing is to learn by our mistakes and to avoid their perpetuation. Mankind has always made progress by the method of trial and error. He who makes no mistakes does nothing. Though not meant literally there is much truth in the aphorism of John Hunter "Don't think, try." It is of course necessary both to think and to try and then to think again. In these processes of thought and trial the general practitioner has been always active. Experimental studies always require verification by practitioners of medicine before they can gain lasting recognition. Practice is, and has always been, the crucial test of theory.

In the brief space allotted to me here I desire to emphasize certain points that bear upon the general practitioner's relation to endocrinology. I shall refer especially to the major endocrin syndromes that are now well established, to the complexity of the so-called multiglandular syndromes, to the significance of the balanced activity of the endocrin glands for normal structure and function, to the general practitioner's special opportunities for observation, to the place of hypothesis in endocrinology, and to the justification of the use of endocrin products in therapy.

2. The Major Endocrin Syndromes

It is to practitioners of medicine that we owe the recognition and description of at least the majority of the syndromes now known to be endocrin in origin. I need only refer to Dr. F. H. Garrison's account of the historical development of knowledge concerning the endocrin glands contributed to the present treatise for the proof of this. Addison, Graves, Gull, Marie, Trousseau, and Minkowski, were all practitioners of medicine, and their names, owing to the part they have played in the picturing of classical endocrin symptom-complexes, are inseparably connected with the history of endocrinology.

No attempt to give full descriptions of the major endocrin syndromes shall be given here since these will be found fully elaborated in other sections in this work. It may be, however, of use to the general practitioner if I quickly summarize, in a few paragraphs, the states that are now generally recognized as having an endocrin origin.

Addison's Disease and Other Hypoadrenias.—The clinical picture of Addison's disease, with its bronzing of the skin, its asthenia, its digestive disturbances, and its anemia, was shown by the great English clinician, Thomas Addison, to be associated with destructive lesions of the supra-

renal capsule. Since his time we have learned to add low blood pressure and certain other clinical phenomena to this syndrome.

Many years ago I drew attention to the similarity of certain clinical pictures that develop in acute infections, notably in Asiatic cholera, to the symptomatology of Addison's disease, and since then I have repeatedly laid stress upon the development of "hypoadrenia" in such acute infections. This view, it would seem, has met with general acceptance by the medical profession. During the recent war, especially, the recognition of these hypoadrenias that develop in association with acute infectious diseases or after-war traumata became general and was of practical value in treatment.

Exophthalmic Goiter.—The group of phenomena constituting the well known syndrome now known as exophthalmic goiter was early recognized by general practitioners of medicine in different countries (Parry, Graves, Basedow, Flajani).

The pulsating struma, the tachycardia, and the protrusion of the eyeballs made a triad of symptoms that could scarcely fail to be recognized by acutely observing practitioners. Later on, fine tremor of the fingers was recognized as a fourth cardinal symptom; and, still later, the sweating, the paroxysms of unmotived diarrhea, certain peculiar nervous and mental states, and other phenomena, particularly a whole group of peculiar eye signs, were found often to be present when the syndrome is well developed.

The recognition that this syndrome of exophthalmic goiter is related to disturbance of function of the thyroid gland gave an enormous impetus to endocrin studies. The results of carefully planned medical treatment and, in certain cases, of surgical intervention in exophthalmic goiter are now well known to every practitioner of medicine.

Myxedema.—Equally interesting and stimulating have been the discoveries that cachexia strumipriva, idiopathic myxedema of adults, and sporadic cretinism are due to insufficiency of activity of the thyroid gland. The results of the administration of thyroid substance in the treatment of these states are among the great triumphs of modern medicine; they constitute one of the best examples of so-called "substitution therapy."

General practitioners are now learning to recognize hypothyroidism of mild grade, the so-called thyreopenia (with its clinical manifestations of chronic constipation, a tendency to obesity, sensitiveness to cold, slowing of thought and motion, etc.), with corresponding benefit to their patients.

Gigantism and Acromegaly.—Of somewhat later date was the recognition that giants and acromegalics develop because of overfunction of the hypophysis cerebri, or pituitary gland. The giant and the dwarf have long been known to both lay and medical writers; and even acromegalics, with their remarkable conformation of the head and peculiar skeletal features, were pictured by the older clinicians. It was, however, the clinical

and pathological anatomical studies of Pierre Marie of Paris that proved the relationship of the pituitary gland to these disorders. When the overactivity of the hypophysis cerebri occurs before the epiphyseal lines of the long bones are closed, gigantism develops; when the overactivity does not occur until after the closure of the epiphyseal lines, acromegaly develops.

Important contributions to the surgical treatment of acromegaly have been made, as every one knows, by practitioners of surgery in America, Harvey Cushing, Charles Frazier, and others.

Dystrophia Adiposogenitalis.—In marked contrast with the clinical phenomena accompanying overactivity of the hypophysis cerebri are those that appear when there is underactivity of this gland. A striking form of obesity associated with genital dystrophy and hypotrichosis (the so-called Fröhlich syndrome, or hypophyseal dystrophia adiposogenitalis) is now generally recognized as being due to insufficiency of the pituitary gland.

This insufficiency of the pituitary gland sometimes (though not always) depends upon hypophyseal tumor, in which case deformations of the sella turcica (recognizable in radiographs) and pressure phenomena (symptoms of general increase of intracranial pressure, or, more often, neighborhood symptoms) accompany the syndrome.

Some progress has been made of late in distinguishing the form of obesity due to hypophyseal disease from that dependent upon insufficiency of the thyroid gland or of the sex glands.

Tetany.—The clinical syndrome known as tetany, recognized first in children early in the last century by Scottish and English observers and, later, in adults by French and German clinicians, was carefully studied in many of its manifestations long before its endocrin origin was suspected. The peculiar paroxysms of tonic spasm, the increased excitability of the peripheral nerves, especially of the motor nerves, to galvanic stimulation, the Trousseau phenomenon, the Chvostek phenomenon and many other features of tetany were fully described even before the parathyroid glands were discovered by Sandström. The occurrence of tetany after operations for goitre was commented upon by practical surgeons who did not then know that in addition to removing the thyroid gland at their operations they were removing certain other structures whose absence was responsible for the development of the tetany. In the elucidation of the origin of such post-operative tetany histologists and experimental physiologists and pathologists have made brilliant contributions. Here we see a notable example of the help that the medical practitioner can derive from the work of the experimenter, for it was the latter who showed that removal of the thyroid alone does not cause tetany, that removal of the parathyroids alone is always followed by tetany in human beings and in many animals, and that postoperative tetany depends upon simul-

taneous removal of the parathyroid glands and of the thyroid. But medical practitioners have been quick to avail themselves of the work and results of the experimental pathologists and, during the past few years, they have themselves made still further contributions to the pathogenesis of tetany. They have shown us that certain disturbances of metabolism intermediate between the parathyroid insufficiency and the tetany attacks; and they have brought forward evidence, recently, that indicates that possibly tetany may sometimes develop from similar disturbances of metabolism that have an origin in conditions other than hypoparathyroidism, (e. g. disturbances of acid-base equilibrium; disturbances of mineral metabolism; or intoxications by guanidin bodies).

Status Thymicolymphaticus.—To clinicians who control their work by postmortem examinations we owe the conceptions of those peculiar states now known clinically as status thymicolymphaticus, dependent upon enlargement and, perhaps, upon overactivity of the thymus gland. These states are characterized by peculiar paroxysms or asphyxia and brief unconsciousness in children, by a tendency to glandular enlargement and hypertrophy of the tonsils and adenoids, and by anomalies of dentition and of hair distribution; they are often associated with congenital hypoplasia of the cardiovascular system and of the chromaffin system.

It is in patients presenting the status thymicolymphaticus that we meet with the so-called *asthma thymicum* and the so-called *mors thymica*. Thus children who die in their sleep without apparent cause, or who die suddenly after an injection of antitoxin, during chloroform anæsthesia, or after some minor operation, are often due to a status thymicolymphaticus.

Though the nature of this malady is still far from clear, its relationship to pathological conditions of the thymus would seem to be fairly well established. Recent personal observations have tended to indicate the participation of nucleic and of thymic or lymphatic origin as an etiological factor.

Diabetes Mellitus.—Medical practitioners from the time of Celsus have been acquainted with diabetes mellitus. According to Osler, Aretæus first used the term "diabetes," describing it as a wonderful affection in which the flesh and limbs melted down into urine; and Willis, as far back as the 17th century, described the condition well, stating that the urine was sweet as though it had sugar and honey in it. Before 1800 Rollo had discovered the value of a meat diet in the treatment of diabetes. Our modern conceptions of the disease could not develop, however, until after Claude Bernard had demonstrated in 1857 the glycogenic function of the liver.

Since Claude Bernard's researches, studies of carbohydrate metabolism and of acidosis have made enormous strides. Thanks to the studies of the clinician Minkowski and of the pathologist Opie the significance of the failure of the internal secretion of the pancreas, particularly of the

islands of Langerhans, as a cause of diabetes mellitus has come into view. The pancreas is, accordingly, now regarded not only as the producer of an external secretion into the digestive tube but also as a manufacturer of an internal secretion that is poured into the blood to make the utilization of sugar possible by the tissue cells. If the pancreas be removed experimentally in animals, glycosuria follows; but if pancreatic tissue be successfully grafted even in some remote situation in such animals, the glycosuria will cease. Just how the internal secretion of the pancreas exerts its influence on carbohydrate metabolism has been much discussed and a great deal of experimental work is being done in the hope of settling the question. That many factors, other than the internal secretion of the pancreas, should be considered in connection with diabetes mellitus seems certain. I have myself drawn attention to the possible significance of adrenal factors on the one hand and of proteolytic ferments within the leucocytes and other tissue cells on the other hand. It is to be hoped that in the near future the various factors concerned in mobilization and utilization of glucose in the body will be more clearly established than they are now.

Hypogenitalism (Eunuchism; Eunuchoidism; Menopause).—The world has, from time immemorial, had opportunity to watch the results upon the body and upon the mental state of removal of the testicles in males. Since the introduction of Battey's operation of ovariotomy, we have had manifold opportunity for observing, also, the effects of spaying in women, and particularly of studying the artificial menopause thus produced.

The effects of castration in man, especially if the operation be done in childhood, are very characteristic. The studies of the sect known as the Skopzi are now familiar to all. An excellent account of these *eunuchs* is given in the monograph by Tandler and Gross.

The internal secretion of the gonads, functioning normally, seems to determine: (1) the time of closure of the epiphyseal lines in the long bones, and (2) the development of the secondary sex characters, both physical and mental.

Males castrated in childhood often grow to be very tall persons and to have long legs and arms on account of the failure of the epiphyseal lines in the long bones of the extremities to close at the usual time. The facies of eunuchs is characteristic. There is a sleepy look to the eyelids. The distribution of the hairs on the body is abnormal. Thus, the supercilia tend to be scanty especially lateralward; the hairs in the axillæ—the so-called hirsi—are scanty, as are those on the mons Veneris; and the distribution of the hairs in the latter position is prone to assume the character of that of the opposite sex. The mental state of the eunuch (timidity, lack of initiative and of aggressiveness) is well known. Even the breasts may approach the feminine type (gynecomastia).

Physical and mental states similar to those characteristic of eunuchs are occasionally met with in males in whom there has been a hypoplasia of the gonads, or an injury to these structures from disease as in the testicular atrophy following the orchitis of mumps. Persons presenting such abnormal states are known as *eunuchoids*. These males tend to become obese, and in their mental and physical status they suggest the feminine type.

The changes that take place in women at the *menopause* are well known to every practitioner of medicine. The amenorrhea, the tendency to obesity and the gradually developing genital atrophy are the outstanding features. During the adjustment of the organism to the "change of life" certain well known physical and mental disturbances are common. I refer to the hot flushes, the neurasthenic symptoms and the slight mental anomalies with which we are all familiar.

The efforts that have been made to counteract the effects of hypogenitalism by substitution therapy, both medical and surgical, are interesting and may gradually lead to the introduction of therapeutic methods of increasing practical value.

Hypergenitalism (Pseudohermaphroditism; Premature Puberty; Hirsutism).—In contrast with the effects upon the body of an insufficient supply of the internal secretion of the gonads (hypogenitalism), are the phenomena that have been supposed to result from an excessive supply of these substances (hypergenitalism). On this point, however, it is desirable to speak with great reserve, for though the conditions known as pseudohermaphroditism, premature puberty, and hirsutism suggest a hypergenital state, the evidence in favor of it is far less conclusive than we could wish. The conditions that have been found most often to be associated with these remarkable states include: (1) tumors of the suprarenal cortex; (2) tumors, especially teratomata, of the ovaries; and (3) tumors, especially teratomata, of the pineal gland. The future will doubtless determine whether or not the so-called hypergenital states resulting are, in reality, due to an excessive supply of the internal secretions ordinarily manufactured by the gonads, or to substances that closely resemble them.

3. The Multiglandular Endocrin Syndromes

Knowledge of the clinical pictures mentioned above as being dependent upon disorders of the glands of internal secretion have led clinicians to make careful studies of certain more complex clinical syndromes that would seem to point to disorders, existing simultaneously, of two, three or more of the endocrin glands. These clinical pictures have been designated "multiglandular syndromes" or "pluriglandular disorders."

That such syndromes exist there can no longer be any doubt, but the very complexity of their origin makes an analysis of their pathogenesis

particularly difficult. They are discussed as fully as present knowledge warrants in one of the chapters of this treatise.

The general practitioner will find it helpful in studying the atypical cases of endocrin disease to analyze the clinical picture piecemeal, putting down one by one the single symptoms and signs that could be reasonably attributed to overactivity or underactivity of each member of the chain of endocrin glands in the body. There are so many overlappings of function and antagonisms of function in endocrin domains that a final judgment in the assignation of single symptoms and signs to particular glands is often exceedingly difficult. We should be content for the present with objective descriptions of our findings, and, while we may legitimately form hypotheses as to the meaning of these findings, it is desirable that we should clearly differentiate between objective description on the one hand and efforts at pathogenetic interpretation on the other.

My own labors have tended to classify glandular syndromes observed in diseases other than the endocrinopathies, but as the present work is limited to the latter the reader must be referred to my work on the internal secretions.

4. The Significance of Balanced Activities of the Endocrin Glands for Normal Structure and Function

What has been learned of the changes in the body and in nervous and mental states that occur in outspoken disorders of the functions of the endocrin glands has brought medical men to the inevitable conviction that a balanced activity of the internal secretory functions of the several glands is essential for the production and maintenance of what we call normal states. Even the differences in healthy persons in skeletal growth, in facial characteristics, in the appearance of the integument, the nails, the hair and the teeth, in nervous and mental states, and in metabolic activities, may be, in no inconsiderable part, dependent upon variations within normal limits of the functions of the several endocrin glands.

The general practitioner who has familiarized himself with the facts of endocrinology will find it a fascinating study to try to interpret the physical and mental make-up of his patients in the light of these facts. He will be particularly helped in such considerations by a thorough knowledge of the vegetative nervous system, including the sympathetic system proper, and the craniosacral autonomic nervous system. These two reciprocally antagonistic nervous systems are to a large extent played upon by the hormones (or chemical messengers) from the several endocrin glands. Functional pathology in the future will, in all probability, lay even more stress than it does now upon the factors ascribable to the endocrin glandular system on the one hand and to the visceral nervous system on the other.

5. Special Opportunities for Observation by General Practitioners

The general practitioner is particularly favorably situated to make contributions, at least of a certain sort, to the progress of knowledge of the internal secretions. He, more than any other practitioner, has the opportunity to study the influences of heredity on the one hand and of environment on the other in normal and diseased states.

Every general practitioner must already have been impressed with the frequency of the tendency of thyroid disease and of hypophyseal disease, to take two striking instances, to run in families. The careful keeping of family records by general practitioners could doubtless contribute in an important way to our knowledge of hereditary factors in endocrin disease.

The influence of geographic and climatic factors could also be advantageously studied by general practitioners who live in regions in which certain endocrin diseases are particularly prevalent or in regions in which certain others are particularly uncommon. Much has already been done in this connection to throw light upon the origin of goiter and of endemic cretinism. In how far such environmental factors play a part in the origin of other endocrin diseases the future will doubtless disclose.

Another way in which the general practitioner can be helpful is in the studies that he can make of the gradual development of the various endocrin diseases. The general practitioner sees patients before they are ill and has an unusual opportunity for studying the very earliest stages of particular diseases and the slow or rapid evolution of the maladies to their full-blown states.

The general practitioner should, too, be ever on the lookout for new clinical syndromes. They lie undetected all about us. The practitioner who, like Addison or Graves, is able to detect the recurring co-existence of clinical phenomena and to create for us new clinical types is needed just as much to-day as in the past.

6. The Value and Place of Hypothesis in Endocrinology

Though it is important carefully to distinguish objective facts from hypothetical interpretation of facts, I have no sympathy with those who decry all theory and who see no value in the formulation of hypotheses. Even experimenters who decry theory and rail at hypotheses often theorize themselves, though they may not be conscious of it, and frequently on

quite inadequate grounds. There is no scientific advance without the use of hypotheses and theories; indeed, they are among the greatest of the stimuli that spur to accurate observation and experiment—*but only when a sufficient aggregate of data warrants them.*

Pathologists and physiologists, though not averse to formulating theories themselves, often upon insufficient grounds, sometimes infer that the clinician has no right to construct hypotheses or to build up theories. This, in my opinion, is a mistaken attitude. The worker in the clinical sciences must avail himself of all the instruments of science just as does the worker in the pre-clinical sciences. Thus only, in fact, will medical progress by insured.

Differences in capacity of different clinicians will doubtless be responsible for different methods of work. Some men can be most useful by accumulating facts, others by arranging, comparing and trying to interpret facts, still others by subjecting hypotheses to the crucial tests of further observation and experiment.

My own studies, first published in 1903 and 1907, were not true hypotheses, but postulates reached after collating all available data (over five thousand *pro* and *con*) contributed by the various branches of medical science and personal experimental and clinical researches. All these data were then analyzed and used for the upbuilding of the postulate reached, which thus became, so to say, the end-product of all knowledge on the subject.

Salient among the products of my labor, since confirmed by others, were the following postulates: (1) that adrenal secretion is a factor in the formation of oxyhemoglobin in the pulmonary alveoli and so is significant for the processes of oxygenation and metabolism; (2) that thyroid secretion is an important factor in the chemical processes of immunization; (3) that trypsin is an active factor in cellular metabolism and immune chemistry; and (4) that the pituitary gland is neurally connected with the suprarenal and thyroid glands and may influence the secretory activity of these structures. Not only have these working hypotheses, based upon a very large aggregate of facts, biological, experimental and clinical, proved helpful to me in my own work, but they have seemed to elucidate many physiological, pathological and clinical data which previously had admittedly remained obscure.

Each worker in endocrinology makes use of the hypotheses that most appeal to him, but unless these be well sustained by collateral evidence it tends to promote confusion. Before elaborating any theory an investigator or clinician should consider all phases, *pro* and *con* of the problem, and formulate his postulate as a result imposed by existing and well grounded scientific data. Even should new facts compel him to modify or abandon his hypothetical conclusion, the latter has served its purpose if it has stimulated careful observation and experimentation.

7. Use of Endocrin Products in Therapy

The general practitioner is the agent on whom we must rely for the majority of observations upon the effects of endocrin products in therapy. Too often, however, he is not sufficiently critical in his judgment of the effects provoked. There is no field in medicine, perhaps, in which one can be more easily deceived. A man with the best scientific training, with the keenest powers of observation, and with strong critical tendencies, may easily be misled in his judgment of the effects of the remedies he uses in the treatment of disease. And if this be true, it is evident that the man of poorer training, or one who observes inaccurately or is non-critical, will much more often be led to false conclusions. We must, however, work with the natural endowments we have, with the particular training we have received and with the critical powers that we possess; and, though we shall all make many mistakes, advances will, I feel sure, gradually result from the endeavors of conscientious workers in general practice.

The effect of thyroid substances, of hypophyseal substances, of suprarenal substances, of gonadal substances, and the like, are now being watched by practitioners, not only in disorders of the endocrin glands but in other diseases. In recent years it has been possible to work with single substances that have their origin in the endocrin glands, notably with adrenalin (or epinephrin), with pituitrin, and with thyroxin. One of these substances has already been made synthetically, and doubtless, before long, through the untiring activities of biochemists and pharmacists, we shall be supplied with a large number of the synthetic chemical substances that the endocrin glands produce.

Studies of the effects of *epinephrin* in normal and abnormal states have already become very numerous, and the effects of this compound upon the various functions of the body are becoming ever better understood. I need refer only to the use of epinephrin in bronchial asthma, in local anesthesia along with novocain, in heart failure, in arterial hypotension, in senile pneumonia and in the hypoadrenias of various infections to illustrate how important may be the results of the study of the therapeutic effects of a single chemical compound of endocrin origin.

The influence of *pituitrin* upon the uterine contraction during or after labor, upon the intestinal contraction in dynamic ileus, upon the excretion of urine in diabetes insipidus illustrate this action.

The remarkable influence of Kendall's *thyroxin* as an accelerator of metabolism not only in hypothyroid states but in other morbid states as well as in normal conditions is another striking instance of the way knowledge can be advanced by the isolation in purer from of an endocrin product.

Studies of the effects of these purer substances of endocrin origin are particularly valuable for the advance of knowledge. Studies of the effects of the administration of single glands as a whole are also valuable in the same direction. Possibly, too, combinations of substances derived from different glands may advance knowledge, but it will easily be understood that the formation of sound judgment regarding therapeutic influence must be much more difficult in such polytherapy than when a single gland substance or a pure chemical substance is used by itself.

8. The General Practitioner and the Future of Endocrinology

From what I have said it will be clear, first, that the general practitioner can and will profit by every advance that is made in the study of the endocrin glands and their functions, and, secondly, that the general practitioner can himself do much to favor the further development of endocrinological knowledge. Though he himself is primarily interested in clinical studies, he will realize the benefits that must accrue to the clinic from laboratory and experimental studies. He will therefore do all that he can to encourage original investigation, the publication of original researches, and the distribution of text-books and treatises that, from time to time, bring together in organized form the knowledge that has accumulated. It is to be hoped, too, that more general practitioners will associate themselves with societies for the study of internal secretion and will subscribe to journals that bear upon the subject.

Endocrinology, it would seem, has already attained to a development that justifies the establishment in our medical schools of professorships and departments, or at least sub-departments, that deal with this particular domain. The establishment of such chairs and the endowment of researches in such departments or sub-departments would go far toward quickly advancing knowledge in this field.

If the general practitioner will use his influence in the several directions mentioned, and will himself take a personal interest in accurate diagnosis and carefully controlled therapy of the diseases of endocrin origin, he will give help that is much needed at this time.

SECTION XVII

Charts of Endocrinopathies

Intended for Preliminary Orientation in the Classification of Disorders Attributed to the Endocrine Glands

Thomas P. Sprunt

Introductory Note—Thyroid Gland—Parathyroid Glands—Hypophysis Cerebri (Pituitary Gland)—Epiphysis Cerebri (Pineal Body)—Suprarenal Glands as a Whole—Chromaffin System—Interrenal System—Sex Glands or Gonads—Thymus—Pancreas.

Charts of Endocrinopathies

Intended for Preliminary Orientation in the Classification of Disorders Attributed to the Endocrin Glands

THOMAS P. SPRUNT

BALTIMORE

Introductory Note

In the present confused state of knowledge concerning the normal functions of the endocrin glands it would be futile to attempt to make, with any pretence to scientific accuracy, a full classification of the symptoms that may arise from disturbances of their functions. As a working guide for quick reference, these charts may, however, serve a practical purpose. They have been included in this work in response to requests from practising physicians for tabulated, easily accessible data.

The difficulties of attempting such an arrangement of symptoms and signs may be readily appreciated when one considers, for example, the conflicting views set forth in the literature concerning the functions of the epiphysis cerebri and of the thymus. Even their inclusion among the glands of internal secretion is questioned by many and hence the source of the clinical symptoms associated with lesions of these structures will be ascribed to their malfunction or to other factors according to the various opinions entertained. Again, very little is known concerning the states of overfunction of the parathyroid glands and of the chromaffin system. Data from some very interesting cases recently described have, nevertheless, been placed in a hyperparathyroid column. The association of enlargement of the parathyroid glands, chronic renal disease and extensive calcium deposits is very interesting, though we do not yet know the primary seat of the disease. The question of unity in etiology in tetany and the tetanoid states as evidences of parathyroid deficiency is also a live one. In deference to prevailing opinion, diabetes mellitus has been placed under the heading of the pancreas.

No attempt has been made to present a complete list of symptoms in any table. To do so would tend to defeat the purpose of such an arrangement. Data that are less important, less frequent, or very questionable have been enclosed in brackets [ ]. It will be remembered, of course, that in no single case would we expect to find all the symptoms enumerated under a given heading, and, further, that, in view of the well recognized

correlation between the various glands of internal secretion, we may expect to encounter many mixed cases. It is important also to note the not infrequent occurrence of cases of dysfunction of an endocrin gland in which there occur certain features suggesting overfunction on the one hand and other features suggesting, on the other hand, underfunction of the same gland.

1. THYROID GLAND

	States of Overfunction	*States of Underfunction*
Endocrin System	Diffuse, vascular thyroid struma or nodular struma. Hypersensitiveness to adrenalin and to thyroid extract. [Hypogenitalism]. [Enlarged thymus].	Aplastic or atrophied thyroid, or colloid struma. No increased sensitiveness to adrenalin. Thyroid extract well borne. [Compensating hypophyseal hypertrophy with enlarged sella turcica.]
Metabolism	Accelerated basal metabolism. Undernutrition. Loss of weight. Diminished carbohydrate tolerance. [Disturbed protein and mineral metabolism.]	Retarded basal metabolism. Obesity. Increased carbohydrate tolerance. Hypothermia.
Bones, Joints and Muscles	Delicate bony structure. Long, slender fingers. [Increased mobility of joints.]	Retardation of bony growth. Defective development of ossification centers. Short, thick or deformed bones. Short, thick fingers with blunt ends.
Respiratory System	Shallow breathing; tachypnea; feelings of dyspnea.	Hypopnea.
Cardiovascular System	Tachycardia; palpitation; vasomotor abnormalities.	Bradycardia; hypotension.
Blood and Hemopoietic Organs	Relative lymphocytosis. Eosinophilia occasionally.	[Leucopenia; lymphocytosis. Eosinophilia.]
Digestive Apparatus	Unmotived attacks of diarrhea; vomiting; nervous indigestion. [Spastic constipation.]	Large tongue; dry mouth; constipation.
Urogenital Apparatus	Amenorrhea; diminished libido and potentia sexualis; pollakiuria; polyuria.	Amenorrhea; diminished libido and potentia.
Nervous System and Psyche	Apprehension; anxiety; [phobias; obsessions]; insomnia; psychomotor activity; fatiguability; tremor; feelings of heat.	Apathy; poverty of thought; drowsiness; psychomotor retardation; feelings of cold.
Organs of Special Sense	Exophthalmos; wide lid slits; von Graefe, Dalrymple, Moebius, etc. [Swollen eyelids.]	Enophthalmos; narrow lid slits.
Integument	Thin, transparent, soft, moist skin; mottled erythema of neck and chest. Smooth, silky hair.	Thick, rough, wrinkled, dry skin. Myxedema. Scanty, brittle, dry, lacklustre hair.

2. PARATHYROID GLANDS

	States of Overfunction (?)	*States of Underfunction Tetany and Tetonoid States*
Endocrin System	Hypertrophied or adenomatous parathyroids (pathological, not clinical).	[Parathyroidectomy with thyroidectomy.] [Postoperative myxedema incidental to thyroidectomy.]
Metabolism	Disturbed calcium metabolism.	Disturbed acid-base equilibrium; disturbed calcium metabolism; decreased calcium in blood [diminished carbohydrate tolerance].
Bones, Muscles Joints	Extensive calcium deposits in muscles and tendons.	Defective bony growth (?).
Respiratory System		Tetany may be induced by deep breathing, even in normal people. Laryngospasm.
Cardiovascular System	Extensive calcification of arteries; hypertension.	Vasomotor disturbances.
Blood and Hemopoietic Organs		
Digestive Apparatus		Enamel defects of teeth. Dilatation of stomach or other gastro-intestinal disturbances (gastric tetany).
Urogenital Apparatus	Chronic renal disease.	
Nervous System and Psyche		Disturbed mental states. Manifest tetany with tonic spasms, carpopedal, laryngeal and occasionally general. Paresthesias. Hyperexcitability of peripheral nerves. Latent tetany with positive signs (Chvostek, Trousseau, Schlesinger, Erb). [Epilepsy.]
Organs of Special Sense		[Tinnitus aurium. Perinuclear cataract.]
Integument		[Skin pallor; dermatographia; erythema; angioneurotic edema; fragile ridged nails. Scanty short hair.]

3. HYPOPHYSIS CEREBRI (PITUITARY GLAND)

	States of Overfunction	*States of Underfunction*
Endocrin System	Enlarged sella turcica, intact or eroded. Occasionally normal sella. [Thyroid struma or atrophy.] [Enlarged thymus.]	Small, closed in sella, or large eroded sella from tumor. Hypogenitalism. [Thyroid or adrenal symptoms.]
Metabolism	Accelerated basal metabolism. Diminished carbohydrate tolerance. Retention of phosphates and lime salts.	Retarded basal metabolism. Obesity. Increased carbohydrate tolerance.
Bones, Joints and Muscles	Bony overgrowth; enlarged oval, elongated or hexagonal facial skull; enlarged frontal sinuses; exaggeration of external occipital protuberance (*x*-ray). [Gigantism before puberty.] Broad, thick, spade-like hands.	Dwarfism, if before puberty, or inversion of sex characteristics. Delayed development.
Respiratory System	Enlargement of larynx with low pitched, hoarse voice. [Chronic bronchitis and emphysema.]	
Cardiovascular System	[Cardiac hypertrophy.]	Hypotension. [Bradycardia.] [Tachycardia.]
Blood and Hemopoietic Organs	[Mononucleosis.] [Eosinophilia.]	
Digestive Apparatus	Spaced incisor teeth (hag teeth). Large tongue.	
Urogenital Apparatus	Hypertrophied external genitalia. Diminished libido and potentia (later). Amenorrhea.	Hypoplastic or infantile genitalia; amenorrhea. Diminished libido and potentia. Polyuria.
Nervous System **General brain symptoms**	Headaches; dullness; apathy. Depression; irritability. [Psychoses] [Epileptiform convulsions.]	Tumor symptoms similar to those of states of overnutrition. Fatiguability. Asthenia. Often slight mental deficiency.
Neighborhood tumor symptoms	Optic atrophy; bitemporal hemianopsia; contraction of visual fields; lesions of other cranial nerves, etc.	Same, if tumor present.
Organs of Special Sense	Eye lesions (see above). Large ears.	Eye lesions.
Integument	Thick, dry, sallow skin with exaggerated wrinkles. Hair, beard and eyebrows heavy and coarse.	Pale, thin, soft skin; [may resemble myxedema or scleroderma]. Hypotrichosis. Heterosexual distribution of hair.

4. EPIPHYSIS CEREBRI (PINEAL BODY)

	Tumors of the Pineal Body
Endocrin System	Hypergenitalism; pressure effect upon hypophysis.
Metabolism	Obesity. [Less commonly cachexia and emaciation.] Increased carbohydrate tolerance.
Bones, Joints and Muscles	Abnormal height.
Respiratory System	
Cardiovascular System	
Blood and Hemopoietic Organs	
Digestive Apparatus	Vomiting.
Urogenital Apparatus	Premature puberty with hyperplasia of genitalia. [Polyuria.]
Nervous System Increased intracranial pressure (internal hydrocephalus)	Headache, vertigo, drowsiness, mental changes, choked disk.
Focal neighborhood symptoms (usually midbrain)	Various cranial nerve palsies, especially III, IV, VI, with diplopia. [Less commonly VII, VIII, and IX; cerebellar symptoms; cerebral peduncle involvement with pyramidal tract lesion.]
Special Senses	Secondarily affected by cranial nerve lesion.
Integument	In children, precocious growth of hair.

5. SUPRARENAL GLANDS AS A WHOLE

	Addison's Disease. State of Underfunction
Endocrin System	Various evidences of disturbance in other glands. Status thymicolymphaticus; hypogenitalism. [Thyroid struma.] [Hypophyseal disease.]
Metabolism	Undernutrition. Low blood sugar with increased carbohydrate tolerance; occasionally decreased tolerance. [Appearance of amino acids in urine.]
Bones, Joints and Muscles	Muscular asthenia; pains in the lumbar region.
Respiratory System	Subjective feelings of dyspnea; Associated tuberculous lesions or scars.
Cardiovascular System	Arterial hypotension; weakened myocardium. [Stenocardiac attacks] [vascular hypoplasia.]
Blood and Hemopoietic Organs	[Lymphocytosis; eosinophilia.] Secondary anaemia.
Digestive Apparatus	Meteorism; abdominal pain and tenderness; anorexia; nausea; vomiting; constipation or diarrhea.
Urogenital Apparatus	Hypogenitalism.
Nervous System	Asthenia; stupor; drowsiness; occasionally insomnia; memory defects [excitation; irritability]. Fainting spells.
Integument	Pigmentation of skin and mucous membranes, varying in tint from dirty yellow to deep dark brown or black, usually diffuse but accentuated in axillæ, about nipples, genitals, extensor surfaces of joints and parts exposed to pressure. Sergent's white line.

6. CHROMAFFIN SYSTEM

	States of Overfunction	*States of Underfunction*
Endocrin System		Status thymicolymphaticus. Hypogenitalism.
Metabolism	[Hyperglycemia (?); decreased carbohydrate tolerance (?).]	Hypoglycemia; increased carbohydrate tolerance.
Bones, Joints and Muscles		Muscular asthenia.
Respiratory System		Feelings of dyspnea.
Cardiovascular System	Arterial hypertension. Vascular sclerosis.	Arterial hypotension. Vascular aplasia. Weakened myocardium.
Blood and Hemopoietic Organs	Hyperglobulia (?).	Lymphocytosis; eosinophilia; secondary anemia.
Digestive Apparatus	Symptoms of disturbed autonomic innervation.	Symptoms of disturbed autonomic innervation.
Urogenital Apparatus	[Chronic renal disease.]	Hypogenitalism.
Nervous System	Various psychoneurotic disturbances.	Adynamia; asthenia; fainting spells.
Integument		Skin pigmentation. Sergent's white line.
Special Senses	[Autonomic nervous system eye signs that are usually associated with hyperthyroidism.]	

7. INTERRENAL SYSTEM

	States of Overfunction (usually in females)		
Endocrin System	Hyperplasia of adrenal cortex, extra interrenal bodies and tumors of interrenal tissues (not detectable clinically until tumors are large).		
	Congenital Form	**Early Postnatal Form**	**Adult Form**
Metabolism		Obesity esp. about hips and abdomen; rapid growth (emaciation and cachexia in later stages).	Obesity (later emaciation and cachexia).
Bones, Joints and Muscles	Reversed sexual characteristics.	Rapid growth; unusual strength (Herculean infants).	Physical strength increased (Virilismus) ("masculine women").
Respiratory System			
Cardiovascular System			
Blood and Hemopoietic Organs			
Digestive Apparatus		[Vomiting and diarrhea in late stages.]	Nausea and vomiting.
Urogenital Apparatus	Pseudohermaphroditismus. (Internal sexual organs of one sex and external genitals resemble opposite sex.)	Pubertas precox; including premature enlargement of genitalia; in girls, mammary gland development and menstruation. In boys, erections and pollutions; change of voice (years before these changes are due).	Irregularity of menstruation, then unusually strong excitability. Hypertrophy of clitoris. [Frigidity in late stage.]
Nervous System and Psyche		Psychomotor activity.	Egotism, overbearing tendency, irritability ("mental hypersthenia"). [Adynamia and melancholia in late stage.]
Integument	Heterosexual type of hair distribution.	Premature development of hair (hirci, crines, barbæ, etc.).	Hirsutismus. Women show mustaches and beards and triangular crines with marked hypertrichosis elsewhere. [General or patchy pigmentation of skin.]

8. SEX GLANDS OR GONADS

	States of Overfunction	*States of Underfunction*		
		Female	**Male**	
			Eunuchs	*Eunuchoids*
Endocrin System	Tumors of ovaries or testes. Hypertrophy of gonads.	Surgical oöphorectomy. Natural menopause. Premature menopause.	Castration. Small thyroid.	Aplastic or hypoplastic gonads. Involvement of other endocrin glands, especially hypophysis.
Metabolism	Early rapid growth.	Obesity. [Retarded basal metabolism?]	Fat deposits on lower abdomen and buttocks, breast region and eyelids.	Similar to eunuchs.
Bones, Joints and Muscles	Rapid growth; partial early gigantism; early closure of epiphyseal lines; premature ossification centers.	Increased height (before puberty).	ncreased height. Tall, thin type [Fat, pudgy type]. Long legs and arms. Small head; broad pelvis. Delayed epiphyseal union.	Similar to eunuchs.
Respiratory System			Small larynx; child-like soprano voice.	
Cardiovascular System		Vasomotor disturbances.		
Blood and Hemopoietic Organs				
Digestive Apparatus	Premature dentition.	Digestive disturbances.		
Urogenital Apparatus	Enlargement of genitalia with premature function (pubertas precox; menstruatio precox). [Osteomalacia.]	Before puberty infantile genitals and secondary sex characters. No mammary development.	Early castration, other sex organs small, no sexual impulse. Late castration, atrophy of prostate, gradual recession of libido and potentia.	Hypoplastic gonads; cryptorchism; sterility; diminished or absent libido and potentia.
Nervous System and Psyche	Mentality modified by premature sexual development.	Nervousness Anxiety; apprehension; [Psychoses].	Lack of normal emotions and will power. Dull, relaxed, clumsy.	Similar to eunuchs.
Integument	Early development of secondary sexual hairy growths.	Lack of secondary sexual development of hair.	Pale sallow wrinkled skin. Trichosis of feminine type.	Pale, delicate finely wrinkled. Hypotrichosis (feminine type).

9. THYMUS

	Status Thymicolymphaticus
Endocrin System	Enlarged thymus (x-ray shadow). Hypoplasia of chromaffin system. [Thyroid struma.]
Metabolism	Rapid changes in body weight. Variable temperature.
Bones, Joints and Muscles	May be either abnormally tall or abnormally short. Anomalies of skull; heterosexual physical configuration (typus femininus in males and typus masculinus in females). Delayed closure of epiphyses. [Juvenile osteomalacia.] Relaxed muscular system.
Respiratory System	Thymic stridor. Asthma thymicum. Asphyxial paroxysms.
Cardiovascular System	Palpitation; dyspnea; cyanosis; sudden death. Congenital hypoplasia of cardiovascular system.
Blood and Hemopoietic Organs	Lymphocytosis; hyperplasia of lymphatic apparatus especially of the internal organs.
Digestive Apparatus	Enlarged middle incisor teeth; disproportion in size between median and lateral incisors. [Long intestine.]
Urogenital Apparatus	Hypoplastic genitalia; cryptorchism.
Nervous System	Insomnia or restless sleep; asthenia; fatiguability.
Integument	Pallor of skin, excessive watery subcutaneous adipose tissue; Heterosexual distribution of hair.

10. PANCREAS

	State of Underfunction. [*Diabetes Mellitus.*]
Endocrin System	Glands which may be spoken of as diabetogenous organs are the pancreas, thyroid, hypophysis, liver, and perhaps the adrenals.
Metabolism	Diminished carbohydrate tolerance with hyperglycemia and glycosuria. [Faulty protein metabolism; defective fat metabolism with lipemia, ketonuria and acidosis.] [Accelerated basal metabolism.] [Rapid emaciation.]
Bones, Muscles and Joints	[Muscular cramps; lumbar pain.]
Respiratory System	[Air hunger of acidosis] [fruity odor of breath.] [Lowered resistance to pulmonary tuberculosis.]
Cardiovascular System	[Arteriosclerosis with intermittent claudication or diabetic gangrene.]
Blood and Hemopoietic Organs	Hyperglycemia.
Digestive Apparatus	Increased hunger and thirst [rapid caries of teeth] [pyorrhea with loss of teeth].
Urogenital Apparatus	Polyuria, nycturia, glycosuria [ketonuria] [albuminuria; cylinduria] [balanitis; decreased libido and potentia].
Nervous System	Neuralgia [neuritis with anesthesias, paresthesias, loss of reflexes and trophic disturbances] [diabetic coma]. Asthenia.
Special Senses	[Early cataract.]
Integument	Dry skin, pruritus [furunculosis].

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